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A *TOP2A*-derived cancer panel drives cancer progression in papillary renal cell carcinoma

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Abstract. The aim of the present study was to investigate the function of the DNA topoisomerase IIα (*TOP2A)* gene and its associated genes in the progression of papillary renal cell carcinoma (PRCC). Online cancer databases, including cBioportal, Oncomine, OncoLnc and Search Tool for the Retrieval of Interacting Genes/Proteins were used to analyze the *TOP2A* gene expression profile, function and regulation network in PRCC. The genes that were significantly co-expressed or mutually exclusively expressed with *TOP2A* were identified. The genes co-expressed with *TOP2A* were defined as a '*TOP2A*-cancer panel', which cooperatively promotes PRCC progression. This gene panel performed well in predicting the prognosis of PRCC. In addition, the *TOP2A*-cancer panel significantly affected the outcome of PRCC compared with clear cell renal cell carcinoma (CCRCC). The protein-protein interaction network of all genes associated with *TOP2A* was also generated. This interaction network may provide foundation for the additional investigation of *TOP2A*. Integrative understating of the *TOP2A*-cancer panel may result in a novel avenue for treatment intervention in PRCC.

Introduction

Cancer is a multi-gene-associated disease; the genes involved in each malignancy compose a 'cancer panel'. This 'cancer panel' results in a complex protein regulation network that is able to determine the patterns of cancer cell behavior (1,2). Therefore, treatments targeting single genes may result in failure, as there are compensatory effects elicited by other genes that occur when a single pathway is blocked (3-5). Therefore, it is necessary to identify these 'cancer panels' in each type of cancer to promote an improved understanding of cell signaling transduction networks and enable the development of higher-efficacy treatments to control cancer cells.

PRCC is the second most common type of kidney cancer. It is also the most malignant type, without any effective therapies (6). Optimal treatment involves surgical removal of the tumor when the disease is in the early stages. However, there remains a lack of treatment options for patients with advanced-stage PRCC (7). Personalized medicine has aimed to distinguish the genetic differences or gene expression pattern alterations in each patient to enable physicians to provide the best treatment for the individual. Cancer is a heterogenetic disease in terms of somatic mutations or gene expression profile alterations in cancer cells (8). Differences in the patterns of gene expression determine the course of treatment to be administered. Therefore, the present study collected data from different cancer databases and integrated the data using a bioinformatics approach to identify a gene panel that affects the progress of PRCC.

DNA topoisomerase IIα (*TOP2A*) encodes DNA topoisomerase, which is an important enzyme that releases the torsional stress when DNA undergoes DNA replication and transcription (9). *TOP2A* actively participates in cellular proliferation (10). It is a critical gene in carcinogenesis (11,12). Additionally, mutations in *TOP2A* are a common cause of the failure of drugs that target the corresponding protein (11). There are numerous data demonstrating that *TOP2A* is involved in a range of cancer types, including breast, endometrial, colon and ovarian cancer (13-16).

The kidney epitheilal cell is a differentiated cell type. *TOP2A* is absent or expressed at low levels in kidney epithelial cells (17). A previous study revealed that *TOP2A* was upregulated in clear cell renal cell carcinoma (CCRCC), and that its expression was predictive of a poor patient outcome (18). Therefore, the present study aimed to identify whether *TOP2A* was also upregulated in PRCC and its function as a cancer

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driver, and attempted to mine data online using a bioinformatics approach to examine the cancer panel associated with *TOP2A* in PRCC.

Materials and methods

Bioinformatics analysis. The Cancer Genome Atlas (TCGA) was joint project launched by the National Cancer Institute and National Human Genome Research Institute, has generated comprehensive, multi-dimensional maps of the key genomic changes in 33 types of human cancer (https://cancergenome.nih.gov/) (19). The present study used the kidney cancer dataset in TCGA. The Oncomine cancer database is a comprehensive cancer database including almost all types of cancer (20). The present study assessed the copy number and gene expression levels of *TOP2A* in Oncomine (https://www.oncomine.org/resource) by searching the gene symbol and cancer type within the 'Cancer vs. Normal Analysis' analysis type filter on 21th March 2017. Furthermore, the outlier analysis tool of Oncomine was used to identify the 'outlier genes' that are only expressed in a number of cancer samples on 21th March 2017. The outlier set in the *TOP2A* positive sample accounted for 5-25% among all samples in the three independent studies (21-23). The survival rate curves were created using OncoLnc (http://www.OncoLnc.org/) on 27th March 2017 (24). The high and low expression groups were set at the upper and lower quartiles, respectively. The high TOP2A expression group was set at >394.46; whilst, the low TOP2A expression group was set at <99.61. Using OncoLnc, the survival curve, the Cox coefficient and the false discovery rate (FDR) were calculated on 27th March 2017. Multiple gene survival analysis was performed using survival tool in cBioPortal for Cancer Genomics (http://www.cbioportal.org) by searching the genes name simultaneously on 1st April 2017 (25,26). The data for the generation of the heat map was downloaded from cBioPortal and hierarchical clustering was performed with MeV software version 4.9.0 developed by GitHub on 11th April 2017 (http://mev.tm4.org/#/welcome). The protein-protein interaction network was completed using the Search Tool for the Retrieval of Interacting Genes/Proteins (STRING, version 10.5) by inputting all the genes on 16th April 2017 (http://string-db.org/).

Statistical analysis. One-way analysis of variance was conducted to analyze variance among multiple groups and a Student-Newman-Keuls test was used for post-hoc comparisons between the groups. Unpaired Student's t-test was performed for the comparison of mean values of two groups. Pearson's correlation analysis was conducted to test the correlation between genes. All these data analysis were performed using Graphpad Prism 5.0 (GraphPad Software, Inc., La Jolla, CA, USA) and the data were presented as the mean ± the standard deviation. Kaplan Meier analysis was used to compare the survival time between two groups with different expression levels of the genes of interest by OncoLnc. The log-rank test was conducted to compare the survival time distribution of the two groups. Hierarchical clustering was conducted for the generation of the gene expression signature heat map using MeV (Version 4.9.0) developed by GitHub, Inc. (San Francisco, CA, USA). Multivariate Cox regression analysis was used for evaluation of the gene expression of the genes assessed here on the patient's risk of mortality. The Cox coefficient, P-value, FDR and gene rank were calculated using the OncoLnc multivariate Cox regressions model tool (24). $P<0.05$ was considered to indicate a statistically significant difference.

Results

TOP2A is upregulated, and high expression of TOP2A contributes to poor outcome in PRCC. The Cancer Genome Atlas dataset of renal cell carcinoma, which includes 1,017 cases, was analyzed by Oncomine and it was identified that the *TOP2A* gene copy number in PRCC was significantly increased, compared with kidney or CCRCC (Fig. 1A; $P=5.3x10^{-5}$). Whether the increase in gene copy number contributed to the upregulation of *TOP2A* was then assessed. The association between the copy number and its expression level was then analyzed in 23 normal kidney tissues and 11 PRCC tissues. No difference in the expression of *TOP2A* was observed between the PRCC tissues and normal kidney tissues (Fig. 1B; P=0.187). Owing to the heterogeneity of this cancer type, whether the *TOP2A* gene was upregulated only in certain patients with a specific genetic background. Therefore, the Oncomine outlier analysis tool was utilized, and 193 patient tumor tissues from 3 independent studies were analyzed (21-23). It was identified that *TOP2A* was expressed in a subset of patients with high expression of *TOP2A* (Fig. 1C); its association with the outcome of patients was additionally investigated. The difference in survival rates between the *TOP2A* high- and low-expression groups was analyzed using the Cox regression model, and it was identified that *TOP2A* expression was negatively associated with patient outcome (Fig. 1D; $P=1.67x10^{-6}$). It was concluded that *TOP2A* was upregulated in one subset of patients with PRCC, and was predictive of poor prognosis.

Co-expressed/mutually exclusively-expressed genes with TOP2A and their role in PRCC. Pearson's correlation analysis was performed, and it was identified that the expression levels of a large number of genes were correlated with *TOP2A*. Genes with correlation coefficients >0.9 were screened out for additional analysis. The genes co-expressed with the *TOP2A* were: Abnormal spindle microtubule assembly (*ASPM*), exonuclease 1 (*EXO1*), TPX2, microtubule nucleation factor (*TPX2*), kinesin family member 14 (*KIF14*), cytoskeleton associated protein 2 like (*CKAP2L*), *KIF20A*, NUF, NDC80 kinetochore complex component (*NUF2*) and centromere protein F (*CENPF*). The genes that were inversely expressed with *TOP2A* were also probed. Pearson's correlation analysis was performed, and genes with correlation coefficients <-0.3 were selected. These genes included tumor protein P53 inducible nuclear protein 2 (*TP53INP2*), Rab interacting lysosomal protein (*RILP*), fucokinase (*FUK*), inositol monophosphatase 2 (*IMPA2*), SPG7, paraplegin matrix AAA peptidase subunit (*SPG7*) and synaptogyrin 1 (*SYNGR1*). A heat map for visualizing the association between these genes was generated. The gene expression profiles in the patient tumor tissues were characterized, and the two gene sets of genes that were mutually exclusively-expressed in tumor tissues were identified (Fig. 2).

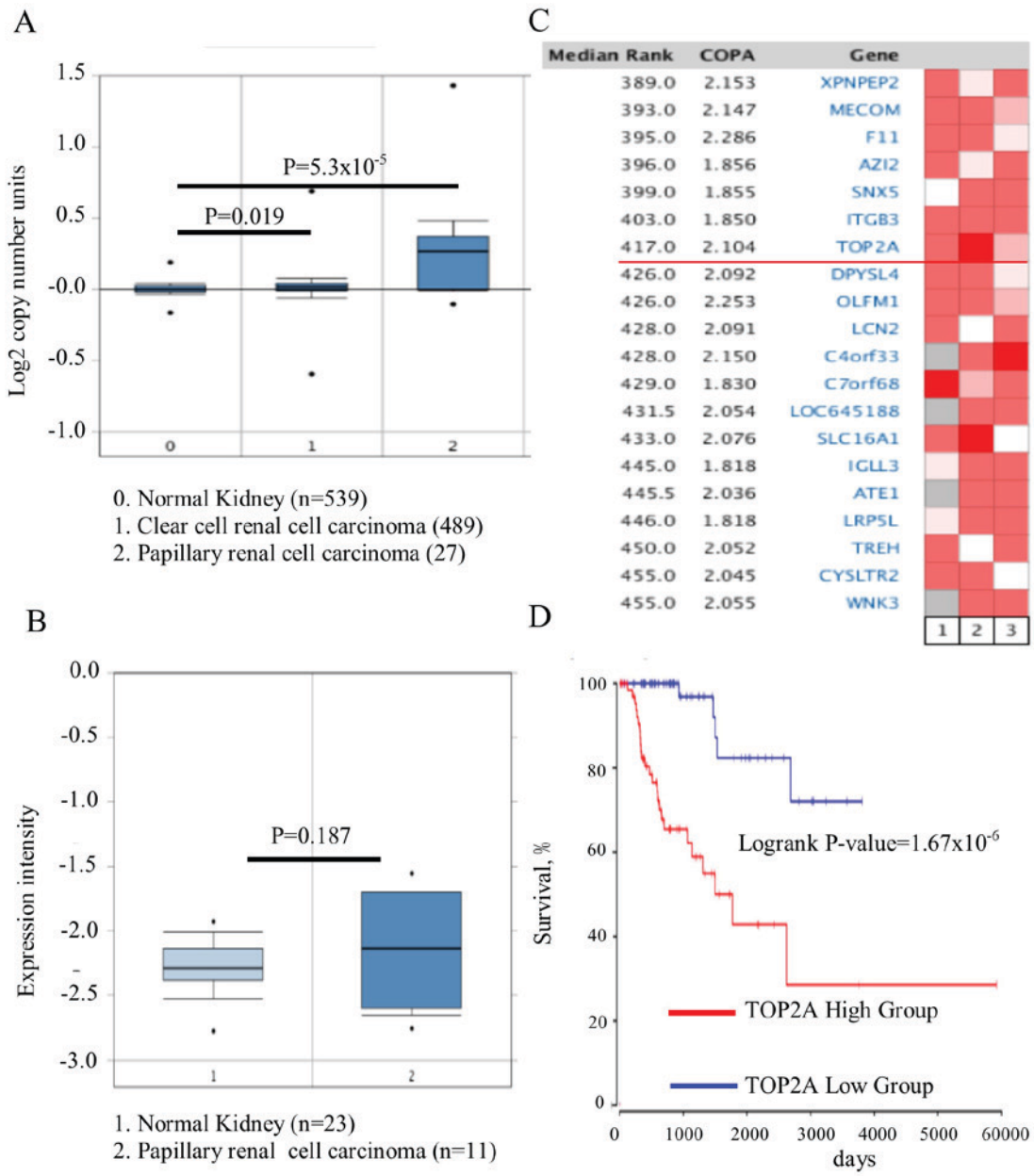

Figure 1. *TOP2A* is dysregulated in a subset of patients with PRCC and predicts poor outcome. (A) The copy number of *TOP2A* in PRCC was increased, compared with clear cell renal cell carcinoma and normal kidney tissue. (B) There was no significant differential expression of *TOP2A* in the tissues of PRCC and normal kidney cells. (C) *TOP2A* was upregulated in a subset of patients with PRCC using outlier analysis. (D) High expression of *TOP2A* in patients with PRCC predicts a poor survival rate. *TOP2A*, DNA topoisomerase IIα; COPA, copy number. PRCC, papillary renal cell carcinoma.

Furthermore, the two sets of genes were compared in CCRCC and PRCC. Not only was the expression level rank but also the Cox regression coefficient was significantly lower in the CCRCC compared with PRCC (Table I).

TOP2A cancer panel predicts prognosis in PRCC. The roles of the genes in the *TOP2A* 'panel' in PRCC remain elusive. A survival curve analysis for each gene between their respective high- and low-expression groups was performed. It was identified that these genes were good prognostic markers. Notably, these genes performed better in predicting prognosis of the patient in PRCC compared with CCRCC (Table I). *ASPM*, *TPX2*, *CENPF*, hyaluronan mediated motility receptor (*HMMR*), *EXO1*, *KIF14*, *KIF20A*, *NUF2*, cytoskeleton associated protein 2 like (*CKAP2L*) predicted the shortest survival time of patients (Fig. 3A-I). However, the upregulation of the mutually exclusive genes (*RILP*, *SYNGR1*, *IMPA2*, *FUK*, *TP53INP2*, *SPG7*) prolonged the patient survival time (Fig. 4A-F). Furthermore, the mutually exclusive gene expression in the patients with TOP2A high expression may counteract the decreased survival time observed in the *TOP2A*-cancer panel gene expression analysis (Fig. 5A-C). The gene interaction network of the *TOP2A*-associated genes was analyzed with the STRING protein interaction analysis tool, and it was observed that the gene co-expressed with *TOP2A* form a 'cancer panel'. The downregulated genes may serve as 'tumor repressor panel' (Fig. 5D).

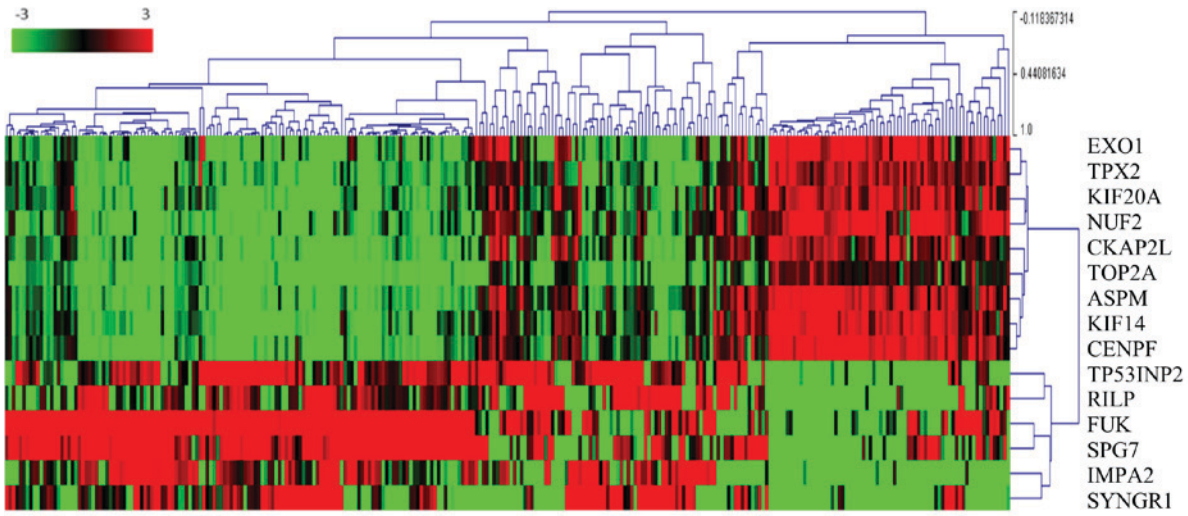

Figure 2. *TOP2A* co-expressed and mutually expressed genes. The heat map depicts the Log2(expression level) of *TOP2A*-associated genes in patients with papillary renal cell carcinoma (each column represents one case). Green to red transition represents the range from -3 to 3 of gene expression after Log2 transformation. The number next to the branches represents the gene expression correlation with other cases. The higher a correlation value is for a case, the more similar the genes expression profile in the same cluster. *EXO1*, exonuclease 1; *TPX2*, TPX2, microtubule nucleation factor; *KIF20A*, kinesin family member 20A; *NUF2*, NUF, NDC80 kinetochore complex component; *CKAP2L*, cytoskeleton associated protein 2 like; *TOP2A*, DNA topoisomerase IIα; *ASPM*, abnormal spindle microtubule assembly; *KIF14*, kinesin family member 14; *CENPF*, centromere protein F; *TP53INP2*, tumor protein P53 inducible nuclear protein 2; *RILP*, Rab interacting lysosomal protein; *FUK*, fucokinase; *SPG7*, SPG7, paraplegin matrix AAA peptidase subunit; *IMPA2*, inositol monophosphatase 2; *SYNGR1*, synaptogyrin 1.

Discussion

Oncogene mutations usually drive carcinogenesis, but gene alteration always results in the regulation of the expression of other associated genes. The expression of these associated genes may comprise a network, and their output may affect the behavior of cancer cells. These genes serve a vital role in establishing the properties of different types of cancer usually was defined as 'cancer panels' (27). The two most common types of kidney cancer are CCRCC and PRCC (28). CCRCC is sensitive to chemotherapeutics and patients generally exhibit improved outcomes following therapy compared with without therapy (29). However, PRCC often exhibits resistance to current chemotherapeutics (30). It was reported that *TOP2A* was upregulated in prostate cancer, breast cancer and serves as an indicator of a poor outcome (11,31). Previously, a number of studies have revealed that *TOP2A* is upregulated in CCRCC and is a poor predicative marker for pgrognosis (18,32). However, to the best of our knowledge, there are no stdies on whether *TOP2A* is dysregulated in PRCC. The present study identified that *TOP2A* is upregulated in kidney cancer and is significantly increased in PRCC compared with CCRCC. Additionally, *TOP2A* functioned well in predicting the prognoses of patients with PRCC compared with in CCRCC. This result indicated that *TOP2A* may be involved in PRCC.

The 'cancer panel' established in the present study included genes that were involved in similar biological functions and contributed to cancer progression. These genes function concomitantly to affect the behavior of cancer cells. Identification of the associations between these genes and their interaction network may enable an improved understanding of how *TOP2A* causes the development of PRCC. To intervene in cancer progression, the interruption of one driver gene is not sufficient for the complete inhibition of cancer progression. Integral disruption of all of the genes involved in cancer progression is more important for the successful treatment of cancer, than focusing on a single target gene. Therefore, the present study analyzed the genes that were closely associated with *TOP2A*. Genes that were significantly co-expressed with *TOP2A* were selected, and it was hypothesized that these genes may be simultaneously involved in PRCC progression. To confirm the function of these genes in PRCC, the survival curves for the high- and low-expression groups of each gene were generated. Notably, it was identified that the expression of these genes significantly reduced the survival time of patients. Therefore, the expression levels of these genes was not only associated with *TOP2A*, but also upregulation of these genes would reduce the survival rates of the patients. This result indicated that *TOP2A* may prompt PRCC progression in conjunction with other genes; however, whether *TOP2A* regulates the expression of these genes requires additional investigation.

Considering the genes in the 'TOP2A-cancer panel', the present study aimed to identify the processes they are involved in, and to understand how these genes function together to determine cancer cell properties. The *ASPM* gene is closely associated with spindle function, which is involved in cell mitosis (33). The *TPX2* gene is a spindle assembly factor that servers as a critical role in G_2/M transition of cell cycle (34). The *HMMR* gene encodes a protein that forms a complex with *BRCA1/2*, which promotes cell proliferation and increases the risk of cancer (35). The *CENPF* gene is required for chromosome segregation in cell mitosis, which regulates DNA replication and cell cycle progression (36). *EXO1* encodes an exonuclease that is responsible

Table I. Comparisons of Cox coefficient, P-value, FDR and gene rank between the papillary renal cell carcinoma and clear renal cell carcinoma samples using a Cox regression model.

A, Co-expressed genes				
Gene/cancer types	Cox coefficient	P-value	Corrected FDR	Rank
TOP2A				
PRCC	1.238	5.10×10^{-11}	2.14×10^{-7}	3
CCRCC	0.259	3.00×10^{-3}	1.22×10^{-2}	4,086
TPX2				
PRCC	1.23	4.20×10^{-10}	3.21×10^{-7}	21
CCRCC	0.34	2.20×10^{-4}	1.57×10^{-3}	2,332
EXO1				
PRCC	1.039	2.90×10^{-9}	9.93×10^{-7}	48
CCRCC	0.16	6.00×10^{-2}	1.27×10^{-1}	7,875
KIF14				
PRCC	1.069	1.80×10^{-9}	7.05×10^{-7}	42
CCRCC	0.317	2.50×10^{-4}	1.74×10^{-3}	2,392
KIF20A				
PRCC	1.266	9.60×10^{-11}	2.25×10^{-7}	7
CCRCC	0.377	3.00×10^{-5}	3.39×10^{-4}	1,471
ASPM				
PRCC	1.259	1.10×10^{-10}	2.26×10^{-7}	8
CCRCC	0.286	7.60×10^{-4}	4.16×10^{-3}	3,044
CKAP2L				
PRCC	1.026	1.10×10^{-8}	2.41×10^{-6}	73
CCRCC	0.173	4.00×10^{-2}	9.22×10^{-2}	7,212
NUF2				
PRCC	1.09	5.70×10^{-10}	3.46×10^{-7}	27
CCRCC	0.393	6.40×10^{-6}	1.03×10^{-4}	1,033
CENPF				
PRCC	1.137	3.00×10^{-10}	3.21×10^{-7}	15
CCRCC	0.289	1.10×10^{-3}	5.50×10^{-3}	3,283
B, Mutually exclusive genes				
TP53INP2				
PRCC	-0.77	2.00×10^{-6}	1.30×10^{-4}	253
CCRCC	-0.262	1.70×10^{-3}	7.78×10^{-3}	3,644
RILP				
PRCC	-0.657	1.40×10^{-4}	2.59×10^{-3}	885
CCRCC	0.099	2.20×10^{-1}	3.40×10^{-1}	10,750
FUK				
PRCC	-0.688	1.40×10^{-5}	4.86×10^{-4}	467
CCRCC	0.035	6.40×10^{-1}	7.43×10^{-1}	14,316
IMPA2				
PRCC	-0.678	8.40×10^{-6}	3.41×10^{-4}	403
CCRCC	-0.319	1.70×10^{-4}	1.29×10^{-3}	2,167
SPG7				
PRCC	-0.917	4.60×10^{-7}	4.56×10^{-5}	165
CCRCC	0.364	1.80×10^{-6}	3.98×10^{-5}	751
SYNGR1				
PRCC	-0.506	1.60×10^{-3}	1.39×10^{-2}	1,891
CCRCC	0.054	5.20×10^{-1}	6.42×10^{-1}	13,508

FDR, false discovery rate; PRCC, papillary renal cell carcinoma; CCRCC, clear cell renal cell carcinoma; *ASPM*, abnormal spindle microtubule assembly; *EXO1*, exonuclease 1; *TPX2*, TPX2, microtubule nucleation factor; *KIF14*, kinesin family member 14; *CKAP2L*, cytoskeleton associated protein 2 like; *KIF20A*, kinesin family member 20A; *NUF2*, NUF, NDC80 kinetochore complex component; *CENPF*, centromere protein F; *TP53INP2*, tumor protein P53 inducible nuclear protein 2; *RILP*, Rab interacting lysosomal protein; *FUK*, fucokinase; *IMPA2*, inositol monophosphatase 2; *SPG7*, SPG7, paraplegin matrix AAA peptidase subunit; *SYNGR1*, synaptogyrin 1.

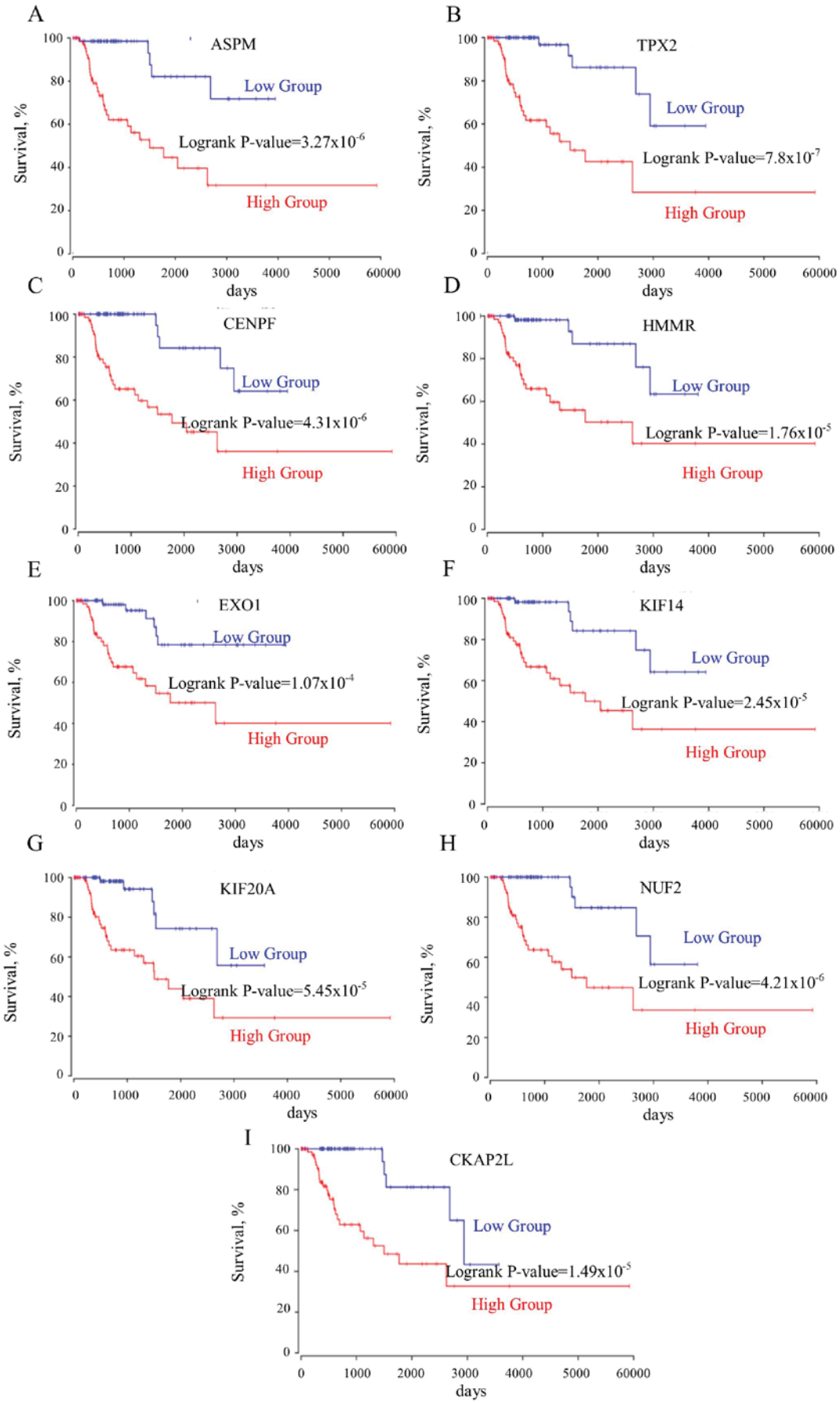

Figure 3. (A-I) All genes co-expressed with *TOP2A* are negatively associated with the survival rates of patients. *ASPM*, abnormal spindle microtubule assembly; *TPX2*, TPX2, microtubule nucleation factor; *CENPF*, centromere protein F; *HMMR*, hyaluronan mediated motility receptor; *EXO1*, exonuclease 1; *KIF14*, kinesin family member 14; *KIF20A*, kinesin family member 20A; *NUF2*, NUF, NDC80 kinetochore complex component; *CKAP2L*, cytoskeleton associated protein 2 like; *TOP2A*, DNA topoisomerase IIα.

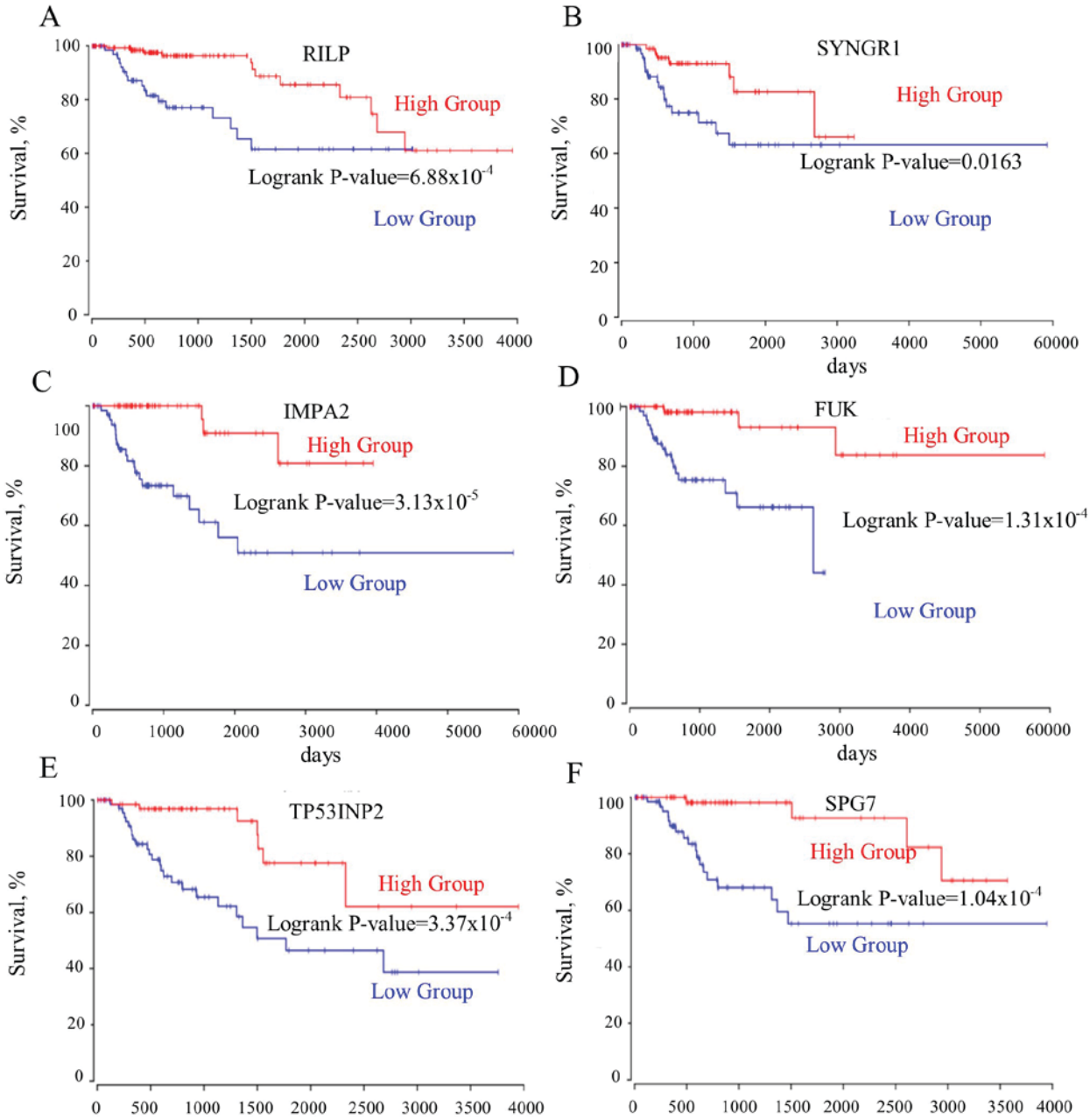

Figure 4. (A-F) All mutually exclusively expressed gene with *TOP2A* are positively associated with the survival rates of patients. *RILP*, Rab Interacting lysosomal protein; *SYNGR1*, synaptogyrin 1; *IMPA2*, Inositol monophosphatase 2; *FUK*, fucokinase; *TP53INP2*, tumor protein P53 inducible nuclear protein 2; *SPG7*, SPG7, paraplegin matrix AAA peptidase subunit; *TOP2A*, DNA topoisomerase IIα.

for DNA mismatch repair (37). *KIF14* contributes to chromosome segregation and spindle formation in the mitosis process (38). *KIF20A* functions as a spindle assembly mediator, resulting in cell division (39). *CKAP2L* is involved in spindle organization (40). *NUF2* regulates chromosome segregation and centromere function in the cell mitosis (41). Therefore, the genes within the *TOP2A*-derived cancer panel function in the regulation of cell mitosis. According to the protein-protein network (Fig. 5D), the results of the present study indicated that *TOP2A* may serve a vital role in the regulation of cell proliferation through interaction with the *TOP2A* cancer panel.

The present study compared the association between the expression levels of these genes with the survival rates of patients with CCRCC and PRCC. It was identified that these genes that coexpressed with *TOP2A* significantly increase the survival rate of patients with PRCC compared with patients with CCRCC. However, the genes that inversely expressed with *TOP2A* decrease the survival rates of patients with PRCC compared with patients with CCRCC, which may provide a method for distinguishing between renal cell carcinoma subtypes by the expression of the *TOP2A* cancer panel genes. The present study identified that *TOP2A* was a vital prognostic marker for PRCC, and the genes involved in the network of *TOP2A* were examined. This network of *TOP2A* genes may assist in understanding how *TOP2A* affects cancer cells, and how targeting these genes may provide an avenue for the treatment of PRCC.

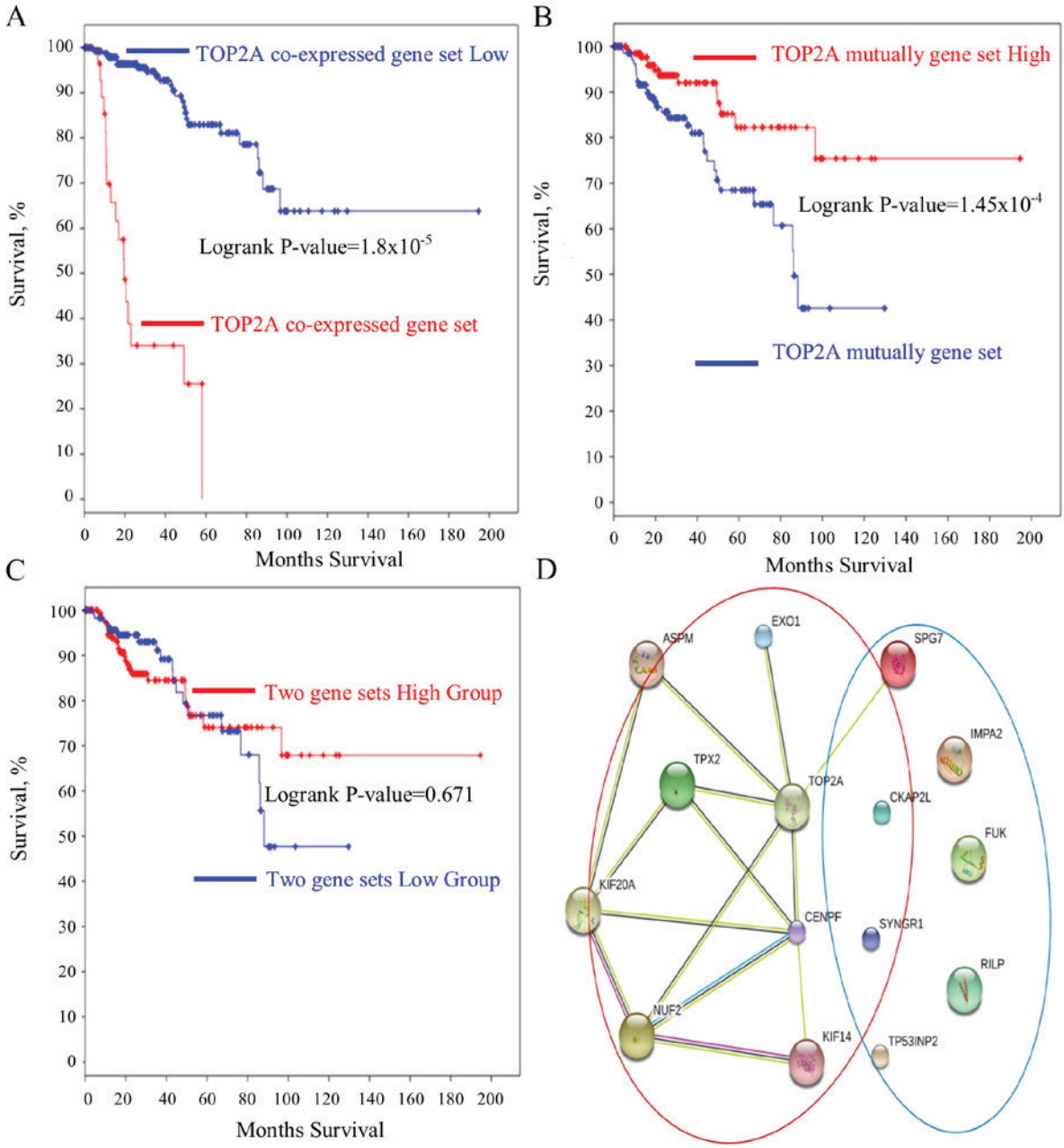

Figure 5. *TOP2A* mutually exclusively expressed genes counteract the *TOP2A* co-expressed genes on reducing the survival rates of patients and the protein-protein interaction network between all genes of *TOP2A*-cancer gene set. (A) The survival rate of the patients with all *TOP2A* co-expressed gene upregulated. (B) The survival rates of the patients with all *TOP2A* mutually exclusively expressed gene upregulated. (C) The survival rates of patients with all the *TOP2A*-associated genes upregulated. (D) The protein-protein interaction network of all genes. Genes co-expressed with TOP2A are included in the red circle. Genes mutually exclusively expressed with TOP2A are included in the blue circle. *TOP2A*, DNA topoisomerase IIα.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

MY and ZH collected data and developed the methodology. DW, ZI and XC interpreted the results. MY and JL designed the work and wrote the manuscript.

Ethics approval and consent to publish

This study reinterpreted the data deposited in TCGA and GEO without releasing the information of patients. According to TCGA publication guidelines, there are no restrictions on the use of TCGA data for research purposes.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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