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Comprehensive Analysis of Driver Genes in Personal Genomes of Clear Cell Renal Cell Carcinoma

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Abstract

Aim: To characterize personal driver genes in clear cell renal cell carcinoma independent of somatic mutation frequencies. **Methods:** Personal cancer driver genes were predicted by Integrated CAncer GEnome Score in 417 patients with clear cell renal cell carcinoma using 26 786 somatic mutations from The Cancer Genome Atlas, followed by an integrated investigation on personal driver genes. **Results:** A total of 233 personal driver genes were determined by Integrated CAncer GEnome Score. The coexpression network analysis found 5 coexpressed modules. The blue module was significantly negatively correlated with all 5 clinical features, including cancer stage, lymph node metastasis, distant metastasis, age, and survival status (death). *CTNNB1*, *TGFBR2*, *KDR*, *FLT1*, and *INSR* were the hub genes in the blue module. The expression of 79 personal driver genes was significantly associated with clinical outcomes of patients with clear cell renal cell carcinoma. **Conclusions:** The set of personal driver genes sheds insights into the tumorigenesis of clear cell renal cell carcinoma and paves the way for developing personalized medicine for clear cell renal cell carcinoma.

Keywords

clear cell renal cell carcinoma, personal driver gene, iCAGES

Abbreviations

ccRCC, clear cell renal cell carcinoma; DM, distant metastasis; GO, gene ontology; iCAGES, Integrated CAncer GEnome Score; KEGG, Kyoto Encyclopedia of Genes and Genomes; LNM, lymph node metastasis; mRNA, messenger RNA; PPI, protein–protein interaction; RCC, renal cell carcinoma; STRING, Search Tool for the Retrieval of Interacting Genes/Proteins; TCGA, The Cancer Genome Atlas; VEGF, vascular endothelial growth factor.

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Introduction

Renal cell carcinoma (RCC) originates from the renal epithelium and accounts for over 90% of cases with cancer in the kidney.[1] Renal cell carcinoma is classified into 16 histological and molecular subtypes, with clear cell RCC (ccRCC) the most common and accountable for most cancer-related deaths.[2] Cancer is a disease caused by acquisition of somatic driver mutations that confer growth advantage to cancer cells.[3] Driver genes that carry driver mutations play a pivotal role in the formation and progression of cancers and have become a focus of cancer genomics studies.

Over the past 5 years, numerous studies have been conducted to characterize the driver genes and mutations using population-scale genomics data in ccRCC.[4-7] Sato *et al* reported an

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integrated study of more than 100 cases with ccRCC and found defective Von Hippel-Lindau tumor suppressor (VHL)-mediated proteolysis was a common feature of ccRCC, the phosphatidylinositol-3-kinase (PI3K)/Akt and the mammalian target of rapamycin (mTOR) signaling (PI3K/AKT/mTOR pathway), the Kelch-like-ECH-associated-protein 1/Nuclear factor erythroid 2–related factor 2/cullin-3 (KEAP1-NRF2-CUL3) apparatus, DNA methylation, p53-related pathways, and messenger RNA (mRNA) processing, which are recurrently mutated pathways and components in ccRCC.[4] Creighton *et al*[5] surveyed more than 400 tumors using different genomic platforms and identified chromatin modifier genes such as the VHL/Hypoxia-inducible factor (HIF) and PI(3)K/AKT pathways frequently mutated in ccRCC.[6] Li *et al* applied Oncodrive-FM and Dendrix to detect driver genes with middle or low mutation frequencies and performed an integrated study on the 342 driver genes; many driver genes are aberrantly expressed, demethylated, and associated with cancer prognosis, providing potential prognostic biomarkers and targeted therapies for patients with ccRCC.[7] These studies shed insights into the pathogenesis of ccRCC.

Integrated CAncer GEnome Score (iCAGES) is a novel statistical framework that infers driver variants by integrating contributions from coding, noncoding, and structural variants; identifies driver genes by combining genomic information and prior biological knowledge; and then generates prioritized drug treatment.[8] The iCAGES consists of 3 consecutive layers. The first layer prioritizes personalized cancer driver coding, noncoding, and structural variations. The second layer associates these mutations to genes using a statistical model with prior biological knowledge on cancer driver genes for specific subtypes of cancer. The third layer generates a list of drugs targeting the repertoire of these potential driver genes. In this study, we explored driver genes in 417 personal ccRCC genomes and performed integrated analyses on them using different genomic and proteomic data from The Cancer Genome Atlas (TCGA)[6] and Search Tool for the Retrieval of Interacting Genes/Proteins (STRING) databases.[9] We uncovered a set of cancer driver genes, and many driver genes were coexpressed with other driver genes and associated with clinical outcomes of patients with ccRCC. Our study points out the importance of characterizing driver genes to facilitate cancer diagnosis and personalized therapy in ccRCC.

Materials and Methods

Prediction of Driver Genes, Personalized Treatments

Of the 537 ccRCC samples in TCGA database, 417 underwent exome sequencing and 26 786 somatic mutations were detected.[6,10] For each patient with ccRCC, driver genes and personalized treatments were predicted by iCAGES[11] (http://iCAGES.wglab.org/). Parameters were set to default values. Genes with iCAGES GeneScores above 0.5 were considered as driver genes in personal cancer genomes. Driver genes were compared among patients with ccRCC having different cancer stages and metastatic statuses. Drugs with iCAGES GeneDrugs above 0.5 were regarded as the personalized treatment for the patient with ccRCC.

The Enrichment of Gene Ontology Terms and Kyoto Encyclopedia of Genes and Genomes Pathway Analysis

To characterize the functional enrichment of driver genes, the enrichment of gene ontology (GO) terms was analyzed for all the driver genes on the homepage of geneontology[12] (http://geneontology.org/). The enrichment of Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways was analyzed for all driver genes with STRING[9] (https://string-db.org).

Coexpression Network Analyses

Among the 417 ccRCC samples used in this study, 389 had both RNA-sequencing expression and clinical traits data. Therefore, reads per kilobase of transcript per million mapped reads values of driver genes in the 389 samples of thyroid cancer were used to construct the coexpression modules by the WGCNA package.[13] All parameters were set to default values except for the softpower (7) and threshold (0.0048). The minimum number of genes was set as 10 for the high reliability of the results. The clinical traits of 389 patients with ccRCC were obtained from TCGA database. Module–trait associations were estimated using the correlation between the module eigengene and the phenotype, which enables easy identification of expression set (module) highly correlated with the phenotype.

Protein–Protein Interaction Network Analysis

STRING was applied to build protein–protein interaction (PPI) network using all driver genes in personal ccRCC genomes on the home page of STRING[9] (https://string-db.org). All parameters were set to default values. As for each driver gene, total STRING score was computed by summing combined STRING scores of all PPIs, representing the number of links the driver gene has to other genes.

Survival Analyses

RNAseq and clinical outcome data of 520 patients with ccRCC were retrieved from TCGA to further evaluate whether the expression of driver genes is associated with prognosis in patients with ccRCC. For each driver gene, multivariate Cox regressions that include age, grade, sex, and RNA-seq expression as multivariates were performed using the "coxph" function in R.[14] To prevent extreme RNA-seq values from affecting the Cox regressions, all expression data were inverse normal transformed prior to running the Cox regressions. Then, patients with ccRCC were divided into 2 groups, including the "high-expression" and "low-expression" groups. The former refers to 25% of patients with ccRCC (130 cases) that have the highest RNA expression levels of driver gene, while the latter represents 25% patients with ccRCC (130 cases) that have the lowest RNA expression levels of driver gene. Kaplan-Meier

Table 1. The Number of Genes and Clinical Features Correlated With Modules and Hub Genes in the 5 Modules.

Module Color	Gene Number	Significant Correlation With Clinical Features	Hub Genes
Gray	106	Cancer stage, LNM, DM, and survival status	*LRP1*, *CDK4*, *PLAU*, *PML*, *CDK2*
Turquoise	79	Cancer stage, age, and survival status	*NF1*, *SOS1*, *ROCK2*, *PIK3CA*, *APC*
Blue	21	Cancer stage, LNM, DM, age, and survival status	*CTNNB1*, *TGFBR2*, *KDR*, *FLT1*, *INSR*
Brown	16	Cancer stage, LNM, and DM	*VAV1*, *STAT1*, *PRKCB*, *IL2RB*, *PIK3CG*
Yellow	11	Age	*COL4A2*, *COL4A1*, *GNAI2*, *ADCY3*, *NOTCH1*

Abbreviations: DM, distant metastasis; LNM, lymph node metastasis.

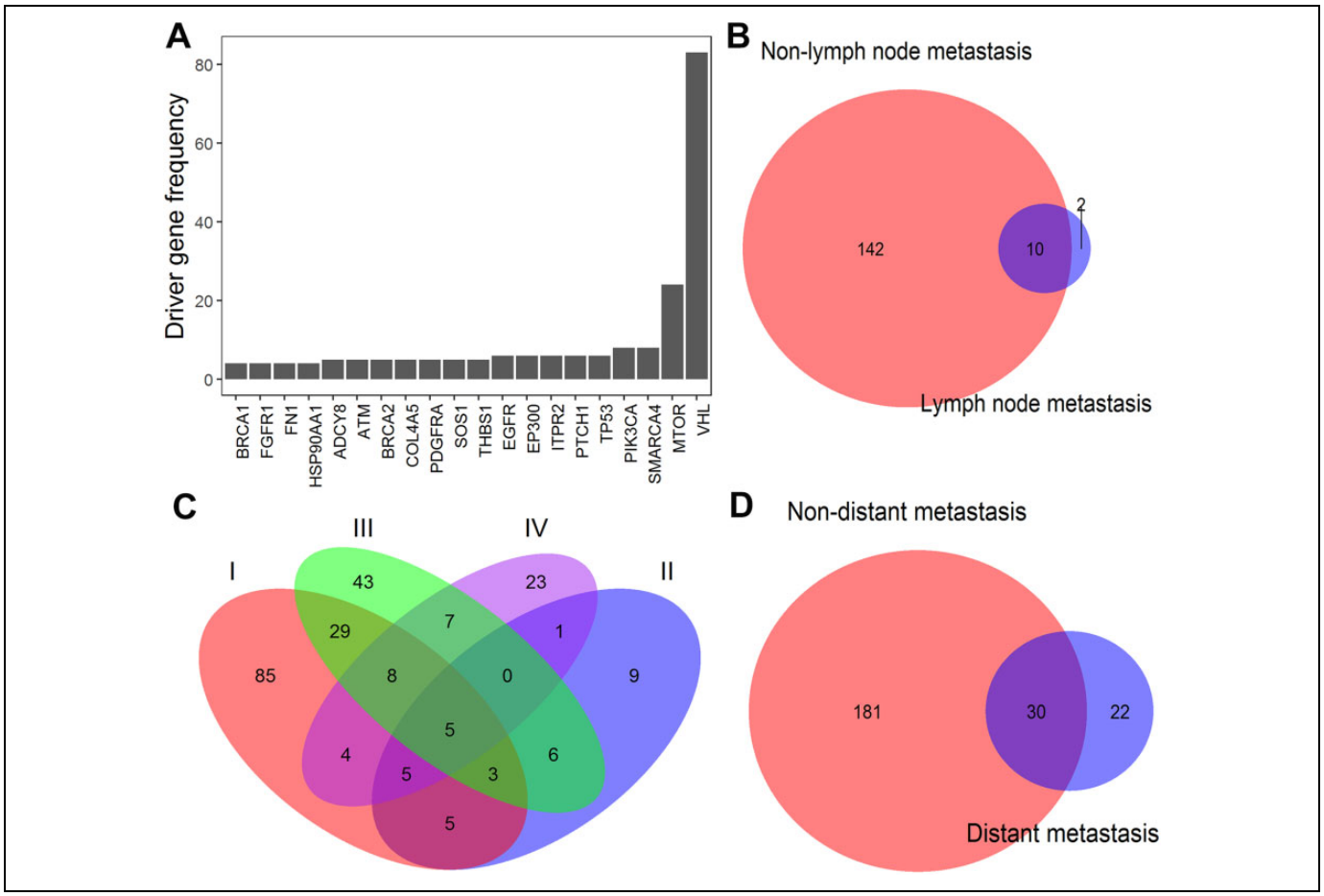

Figure 1. Characterization of driver genes in clear cell renal cell carcinoma (ccRCC). A, The frequencies of top 10 driver genes in 417 ccRCC samples. B, The overlap of driver genes between patients with ccRCC having different lymph nodes metastatic statuses: driver gene. C, The overlap of driver genes in patients with ccRCC at stage I, II, III, and IV: driver gene. D, The overlap of driver genes between patients with ccRCC having different distant metastatic statuses.

plot was made based on patients in the high- and low-expression groups using the survival package[15] on the homepage of oncolnc[16] (http://www.oncolnc.org/).

Results

Driver Genes in Personal ccRCC Genomes

The iCAGES was used to identify driver genes in 417 personal ccRCC genomes. In total, 233 driver genes were determined by iCAGES in 417 patients (Supplementary Table 1). Among them, *VHL*, *MTOR*, *PIK3CA*, *SMARCA4*, *EGFR*, *EP300*, *ITPR2*, *PTCH1*, *TP53*, and *ADCY8* were the 10 most frequently mutated driver genes in patients with ccRCC (Figure 1A). The results support that VHL plays a pivotal role in the tumorigenesis of ccRCC. Of the patients with ccRCC, 59.66% (139/233) had at least 2 driver genes and 35.62% (83/233) of driver genes were predicted in at least 2 patients. The majority of driver genes (64.38%, 150/233) are patient-specific driver genes in ccRCC, such as *CDK4*, *BRAF PIK3CB*, and Hypoxia-inducible

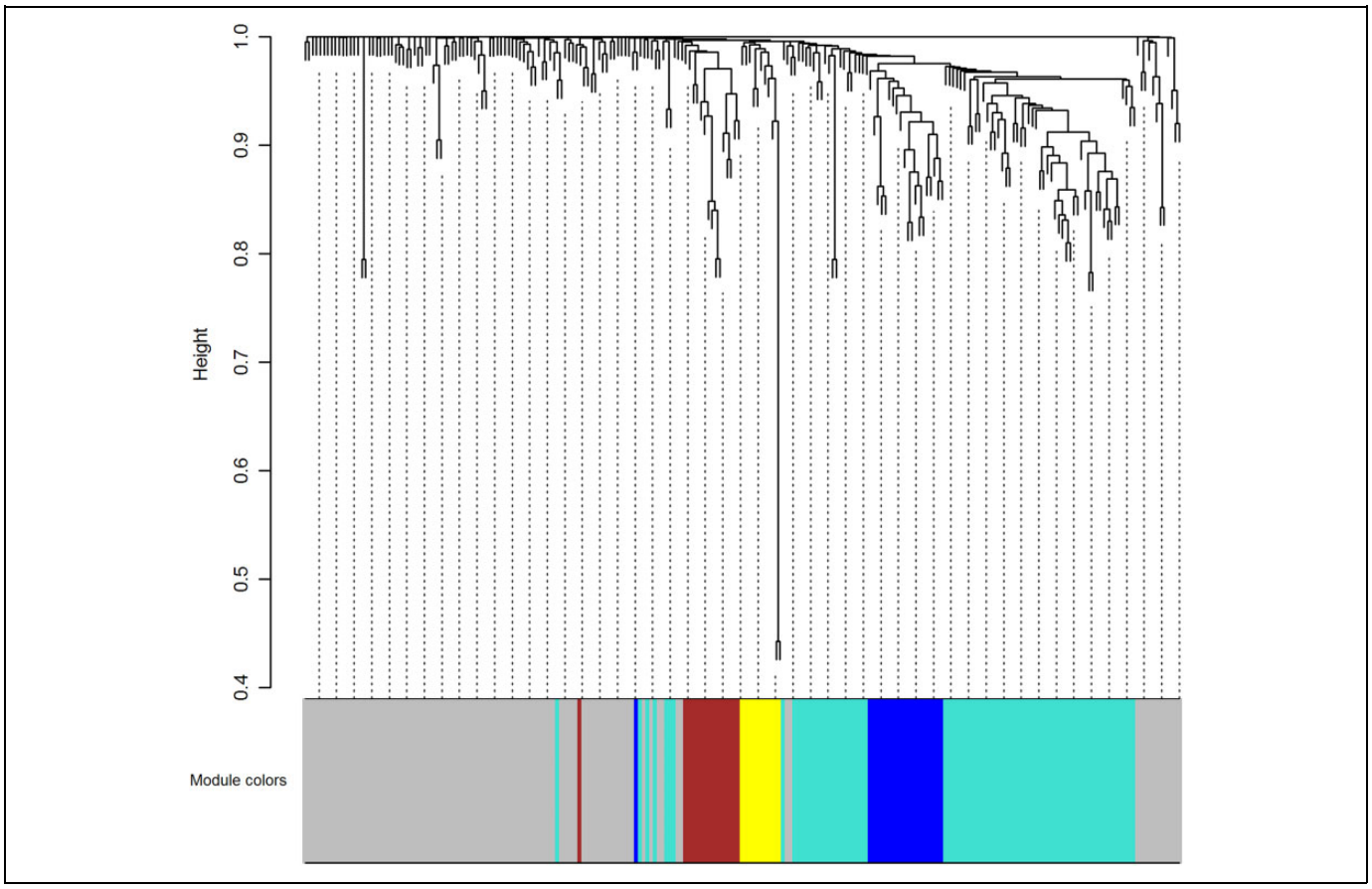

Figure 2. Clustering dendrograms of genes with dissimilarity based on topological overlap, together with assigned module colors. Five coexpression modules were constructed and are shown in different colors.

factor 1 *(HIF-1A)*. Next, we analyzed the association between driver genes and pathological stage, lymph node metastasis (LNM), and distant metastasis (DM), respectively. Sets of driver genes were found to be pathological stage dependent (stage I 85 genes, stage II 9 genes, stage III 43 genes, and stage IV 23 genes; Figure 1B, Supplementary Table 1), LNM associated (LNM-independent 142 genes vs LNM-dependent 2 genes; Figure 1C, Supplementary Table 1), and DM associated (non-DM-associated 181 genes VS DM-associated 22 genes; Figure 1D, Supplementary Table 1).

Gene Ontology and KEGG Pathway Enrichment Analyses in ccRCC

The enrichment of GO terms and KEGG pathways was performed for 233 driver genes, and the driver genes were significantly enriched in 1334 GO terms. The GO terms ranged from cell cycle arrest, angiogenesis, positive regulation of cell cycle, regulation of apoptotic process, Wnt signaling pathway, cell death, regulation of metabolic process, and regulation of cell migration with regulation of transforming growth factor β2 production, entry of bacterium into host cell, positive regulation of metallopeptidase activity, activation of protein kinase A activity, and lung-associated mesenchyme development most enriched for driver genes (Supplementary Table 2). In addition, 233 driver genes were enriched in 148 KEGG pathways, such as pathways in cancer, small cell lung cancer, prostate cancer, pancreatic cancer, glioma, colorectal cancer, RCC, thyroid cancer, glioma, melanoma, bladder cancer, wnt signaling pathway, mitogen-activated protein kinase (MAPK) signaling pathway, mammalian target of rapamycin (mTOR) signaling pathway, Hypoxia-inducible factor 1 (HIF-1) signaling pathway, Hippo signaling pathway, and vascular endothelial growth factor (VEGF) signaling pathway (Supplementary Table 3). The results showed that these driver genes contribute to tumorigenesis and progression of ccRCC mostly through involvement in metabolic processes, epigenetic modifications, and regulation of cancer-associated signaling pathways in ccRCC.

Coexpression Network Analyses in ccRCC

To characterize the coexpression networks of 233 driver genes, WGCNA coexpression networks were built based on the expression correlation of driver genes in 389 ccRCC tissues. As shown in Figure 2, the WGCNA analysis identified 5 distinct gene coexpression modules in ccRCC. These coexpression modules were shown in different colors. These modules ranged from large to small by the number of genes they included, with 106,

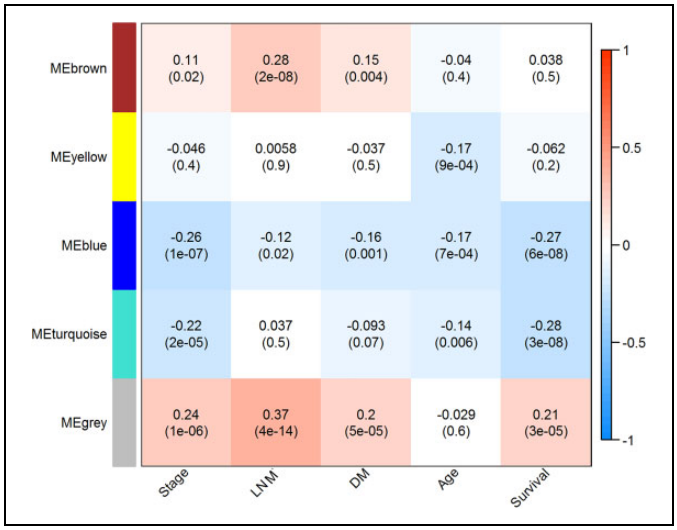

Figure 3. Module–trait associations. Each row corresponds to a module eigengene, column to a trait. Each cell contains the corresponding correlation and *P* value. LNM indicates lymph nodes metastasis; DM, distant metastasis.

79, 21, 16, and 11 in the grey, turquoise, blue, brown, and yellow modules, respectively. The module–trait association analysis indicated that the blue module was significantly negatively correlated with all 5 clinical features, including cancer stage, LNM, DM, age, and survival status (death). The gray module showed significantly positive correlation with cancer stage, LNM, DM, and survival status (death; Figure 3).*CTNNB1*, *TGFBR2*, *KDR*, *FLT1*, and *INSR* were the hub genes in the blue module, while *LRP1*, *CDK4*, *PLAU*, *PML*, and *CDK2* were the hub genes in the grey module (Table 1). These genes have high degrees and large number of interactions with other genes, and therefore, they may act as key genes in the coexpression networks.

Protein–Protein Interaction Network Analysis in ccRCC

In addition to coexpression analysis on driver genes at the mRNA level, we also wanted to know the interactions of driver genes in ccRCC at the protein level. For this, we applied STRING to construct a PPI network using 233 driver genes. A high-degree protein regulates or is regulated by many other proteins, suggesting an important role in the network of interactions. The PPI network for driver genes comprise 233 nodes and 4579 edges, with an average node degree of 3.93 (Supplementary Figure1). The PPI network showed significantly more interactions than expected for a random set of proteins of similar size (PPI enrichment *P* value <.0001). *SRC*, *EGFR*, *EP300*, *TP53*, *CREBBP*, *PIK3R1*, *CTNNB1*, *GRB2*, *PIK3CA*, and *SOS1* are at the core of the PPI network (total STRING score >50; Supplementary Table 4).They are responsible for regulation of cell death, protein metabolic process, regulation of apoptotic process, ERBB2 signaling pathway, and cell differentiation, suggesting they may play key roles in ccRCC.[12]

Survival Analyses in ccRCC

The TCGA RNAseq and clinical outcome data of 520 patients with ccRCC were obtained from TCGA to evaluate whether the expression of 233 driver genes is associated with prognosis in patients with ccRCC. Overall, multivariate Cox regressions analyses showed that the expression of 79 driver genes was significantly associated with clinical outcomes of patients with ccRCC (Supplementary Table 5). The high expression of 31 driver genes indicated a poor survival, such as *AXIN1*, *CDK4*, *CHEK2*, *CTBP1*, *GNAS*, *PLCB3*, *PPARD*, *PSMD7*, *PTCH2*, *RELA*, *RPS6KB2*, *SHC1*, *TNFRSF1A*, *TSC2*, and *XPO1* (Figure 4A). In contrast, patients with high expression of 48 driver genes showed favorable prognosis, such as *ABCB1*, *ATF2*, *BMPR2*, *BRAF*, *G6PC*, *GAB1*, *HSPA8*, *IL6ST*, *NCOR1*, *PLCG2*, *PRKAR1A*, *SOS2*, and *TGFBR2* (Figure 4B). These driver genes might be potential prognostic biomarkers for patients with ccRCC in the future.

Personalized Medicine in ccRCC

Of 417 patients with ccRCC, iCAGES prioritized 29 drugs that target 16 driver genes in 41 patients with ccRCC. The 41 patients included 15, 5, 13, and 8 patients diagnosed at stage I, II, III, and IV, respectively. Thirty-four patients had no distant metastases, while 7 patients had distant metastatic sites. Twenty-six patients showed no metastasis to surrounding lymph nodes, while 2 patients had metastasis to lymph nodes. *PIK3CA*, *EGFR*, *TP53*, *PDGFRA*, and *BRCA1* were the most frequent druggable targets in the 41 patients with ccRCC (Figure 5). Everolimus, GSK2126458, cabozantinib, CUDC-101, erlotinib, MK-2206, paclitaxel, vandetanib, gefitinib, and doxorubicin were the most 10 frequently predicted treatments for the 41 patients with ccRCC (Figure 5; Supplementary Table 6).

Discussion

In this study, for the first time, we applied iCAGES to explore driver genes in personal cancer genomes and performed an integrated study on the 233 driver genes in ccRCC. Several known driver genes have been validated in personal ccRCC genomes such as *VHL* and *MTOR*, which are in line with previously published genomics studies on large cohorts of ccRCC samples.[4-7,17] These 2 genes were the most common driver genes in patients with ccRCC, suggesting *VHL* and *MTOR* may drive the tumorigenesis of ccRCC and become therapeutic targets in ccRCC. By comparing the list of driver genes to annotated oncogene[18] and tumor suppressor gene[19] databases, we found 134 known oncogenes, such as *BRAF*, *FOXO1*, *KRAS*, *HRAS*, *EGFR*, and *PIK3CA*, as well as 74 tumor suppressor genes, such as *SMARCA4*, *TP53*, *ATM*, *BRCA1*, *BRCA2*, and *NOTCH1*. Apart from driver genes detected using population-scale genomics data,[4-7,17] iCAGES predicted a large number of driver genes that are patient-specific in personal ccRCC genomes, such as *RB1*, *GAB1*, and *FOXO1*, which shed insights into the development of personalized medicine in ccRCC.

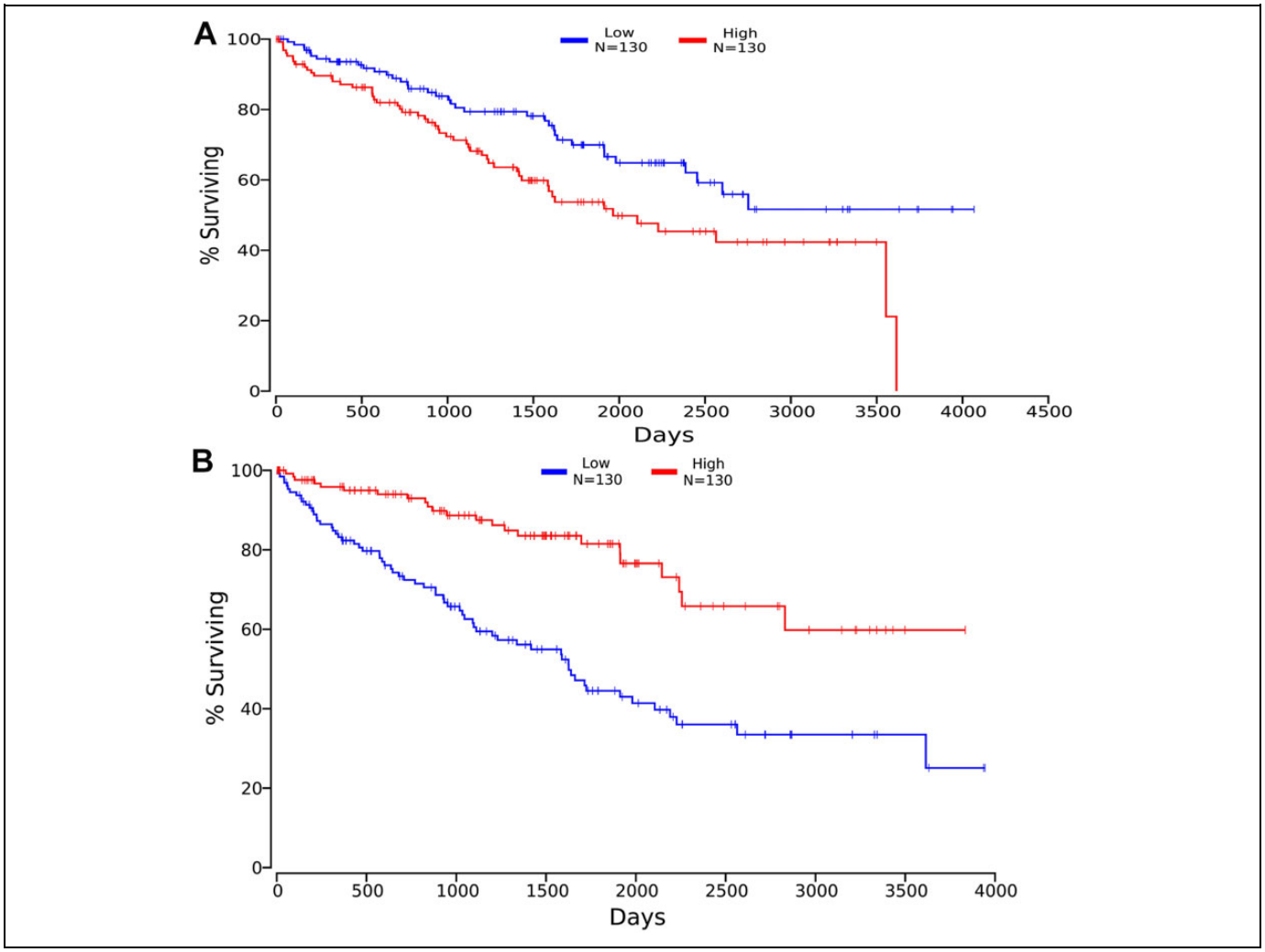

Figure 4. Survival analyses of XPO1 and GAB1 in clear cell renal cell carcinoma (ccRCC). A, Patients with high expression of XPO1 (red) had a relatively poor survival rate in comparison to those with low expression of XPO1 (blue). B, Patients in the high expression group of GAB1 (red) showed better prognosis than those in the low expression group of GAB1 (blue).

WGCNA transforms gene expression data into coexpression module, providing insights into signaling networks that may be responsible for phenotypic traits of interest.[20-22] We identified 5 coexpression modules that relate to clinical traits. The blue module that was negatively correlated with 5 clinical traits and the hub genes *CTNNB1*, *TGFBR2*, *KDR*, *FLT1*, and *INSR* are of importance in ccRCC. The gene *CTNNB1* is a component of the Wnt signaling pathway that has been shown to play an important role in the formation of certain cancers.[23-25] Additionally, we also found a number of hub genes in the PPI network, and the top-ranking genes are responsible for regulation of cell death, protein metabolic process, regulation of apoptotic process, ERBB2 signaling pathway, and cell differentiation, suggesting they may play key roles in ccRCC.[12] The hub genes may eventually serve as biomarkers for detection or treatment in patients with ccRCC.

Of the 233 driver genes, we found 79 genes whose expression levels were significantly related to prognoses of patients with ccRCC. Thirty-one driver genes were associated with poor prognoses in patients with ccRCC, such as *SHC1*, *TNFRSF1A*, *TSC2*, and *XPO1*. Take *XPO1*, for example; *XPO1* has an important function of trafficking over 230 proteins, including tumor suppressors, growth regulator/pro-inflammatory, and antiapoptotic proteins.[26] *XPO1* acts as an oncogenic, antiapoptotic protein in transformed cells and is unregulated in various cancer types.[27-30] In line with our study, high expression of *XPO1* indicates poor survival rates in gastric carcinoma,[29] acute myeloid leukemia,[30] pancreatic cancer,[31] and lung adenocarcinoma.[28] Forty-eight driver genes, such as *GAB1*, *GCNT2*, *LMO7*, and *MTOR*, were related to favorable clinical outcomes in patients with ccRCC. *GAB1* may play an oncogene in cancers.[32-34] Expression of *GAB1* was positively correlated with LNM and TNM stage in intrahepatic cholangiocarcinoma tissues. Downregulation of *GAB1* expression inhibited cell proliferation and invasion in hilar cholangiocarcinoma cells,[32] met-overexpressing colorectal cancer cell line DLD1,[33] and

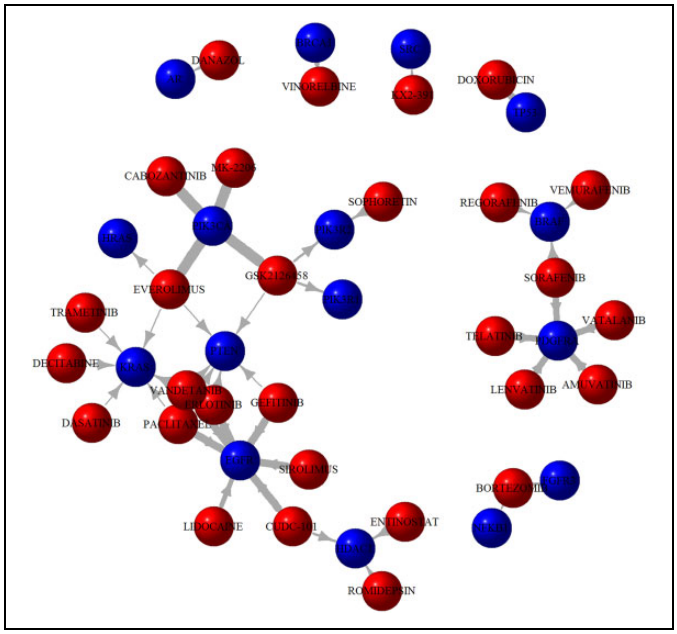

Figure 5. The drug–gene interactions in 41 patients with clear cell renal cell carcinoma (ccRCC). The blue nodes refer to the driver genes predicted by iCAGES. The red nodes were the prioritized drugs that target the driver genes in patients with ccRCC. The edges denote the predicted frequency of drug–gene interactions in patients with ccRCC. The more intensively the drugs interact with driver genes, the more frequently the drug–gene interactions were predicted in patients with ccRCC.

VEGF-induced endothelial cells.[34] Driver genes such as *XPO1* and *GAB1* might become potential prognostic biomarkers for patients with ccRCC in the future.

Conclusions

In summary, we performed an integrative investigation on driver genes identified by iCAGES in personal ccRCC genomes, which deepened our understanding of the etiology of ccRCC. The driver genes and pathways identified herein might open the avenue for the development of prognostic biomarkers and personalized medicine in ccRCC.

Authors' Note

The views expressed in the submitted article are his own and not an official position of the institution or funder. Our study was conducted by mining public data from the TCGA database. It did not require an ethical board approval because it did not contain human or animal trials.

Declaration of Conflicting Interests

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Supplemental Material

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