

ORIGINAL ARTICLE

Identification of Prognostic Related Hub Genes in Clear-Cell Renal Cell Carcinoma *via* Bioinformatical Analysis

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Key words: clear-cell renal cell carcinoma; bioinformatical analysis; differentially expressed genes

Objective To identify new genes that correlate with prognosis of clear-cell renal cell carcinoma (ccRCC) *via* bioinformatics analysis.

Methods The gene expression profiles of 62 ccRCC and 54 normal kidney tissues were available from the Gene Expression Omnibus database: GSE12606, GSE36895 and GSE66272. The differentially expressed genes were screened with GEO2R and J Venn online tools. Functional annotation including Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) was applied to identify the possible function of the hub genes involved in prognosis of ccRCC. In protein protein interaction network (PPI network), the STRING online tool was used to visualize the network of the differentially expressed genes, and the core gene was selected by MCODE App in Cytoscape software. Finally, GEPIA Survival Plot was performed to assess genes associated with worse survival.

Results We totally found 648 differentially expressed genes, including 222 up-regulated genes and 426 down-regulated genes. PPI network showed that in 28 up-regulated genes 7 (*CCNE2*, *CDK1*, *CDC6*, *CCNB2*, *BUB1*,

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TTK and *PTTG1*) enriched in cell cycle and 4 genes (*CCNE2*, *CDK1*, *CCNB2* and *RRM2*) enriched in p53 signaling pathway. GEPIA Survival Plot assay revealed that ccRCC patients carrying *CDK1*, *CCNB2*, *RRM2*, *BUB1*, and *PTTG1* had a worse survival. GEPIA Box Plot showed that *BUB1*, *CCNB2*, *PTTG1*, and *RRM2* were over expressed in the ccRCC tissues in contrast to the normal tissues ($P < 0.05$).

Conclusion ccRCC patients with the four up-regulated differentially expressed genes including *BUB1*, *CCNB2*, *PTTG1*, and *RRM2* might manifest a poor prognosis.

CLEAR-cell renal cell carcinoma (ccRCC) is one of the most common malignant lesion in renal cell carcinoma,^[1, 2] with an estimation of 65 000 new cases per year in the USA.^[3] Even ccRCC patients have improved survival rates through surgical techniques and specific targeted therapy, the predictability of outcome is still poor.^[4] Therefore, to ameliorate the cure rate of ccRCC, more reliable and favorable prognostic factors should be sought as targets.

In this research, we selected the data of GSE12606, GSE36895 and GSE66272 from Gene Expression Omnibus (GEO) datasets to mine differentially expressed genes (DEGs) related to ccRCC prognosis from the whole expression profiling of transcriptome sequencing gene in ccRCC patients and normal individuals using bioinformatical analysis,^[5, 6] to provide useful biomarkers related to survival and some effective target for ccRCC treatment.

MATERIALS AND METHODS

Data downloading and DEG analysis

Three datasets including GSE12606, GSE36895 and GSE66272 were collected from the Gene Expression Omnibus (<http://www.ncbi.nlm.nih.gov/geo>) and generated using GPL570 Platforms. GSE12606, includes 6 ccRCC tumor tissues and 4 normal tissues; GSE36895 includes 29 ccRCC tumor tissues and 23 normal renal cortices, GSE66272 contains 27 primary ccRCC tumor tissues and 27 adjacent normal kidney sample.

DEGs between the cancer and non-cancer tissues from the data of GSE12606, GSE36895 and GSE66272 were screened *via* GEO2R online tools ($|\log FC| > 1.5$ and adjust P value < 0.05), and then were imported to the J Venn online tools (<http://jvenn.toulouse.inra.fr/app/example.html>) to obtain commonly DEGs (c-DEGs) from the three database. DAVID (<https://david.ncifcrf.gov>) was used to detect the association of c-DEGs gene with biological annotation terms (Gene Ontology, GO and Kyoto Encyclopedia of Genes and Genomes, KEGG pathway). When P -value and false discovery rate (FDR)

value are all less than 0.05 unless otherwise specified, it is considered as having statistical significance. The potential correlation was examined by STRING website (<https://string-db.org>) between these c-DEGs (maximum number of interactors=0 and confidence score ≥ 0.4) to obtain the tsv format which was imported to Cytoscape software to analyze the current network. Then the modules of the protein protein interaction network (PPI network) were checked in the MCODE app (degree cutoff=2, max. Depth=100, k-core=2, and node score cutoff=0.2) to filter the core genes and perform re-KEGG pathway analysis. After that, the survival rate of patients having core genes was assessed by GEPIA Survival Plot and the hub genes expression was assayed by GEPIA Box Plot (<http://gepia.cancer-pku.cn/>).

RESULTS

Identification of c-DEGs in ccRCC

We extracted 2032, 1135 and 2826 DEGs from GSE12606, GSE36895 and GSE66272 respectively *via* GEO2R tools. And then we applied J Venn online tool to screen the DEGs in the three database mentioned above and found 648 c-DEGs including 222 up-regulated genes and 426 down-regulated genes in ccRCC tissues (**Fig. 1**).

Results of GO and KEGG pathway analysis

As shown in **Fig. 2**, GO analysis results indicated that ① for biological processes, up-regulated c-DEGs were particularly enriched in response to hypoxia, adaptive immune response, and down-regulated c-DEGs in excretion; ② for cell components, up-regulated c-DEGs were significantly enriched in membrane, extracellular space, extracellular region and cell surface, and down-regulated c-DEGs in extracellular exosome, apical plasma membrane, basolateral plasma membrane, integral component of plasma membrane and integral component of membrane; ③ for molecular function, up-regulated c-DEGs were enriched in protein binding and down-regulated in anion antiporter activity.

KEGG analysis demonstrated that up-regulated

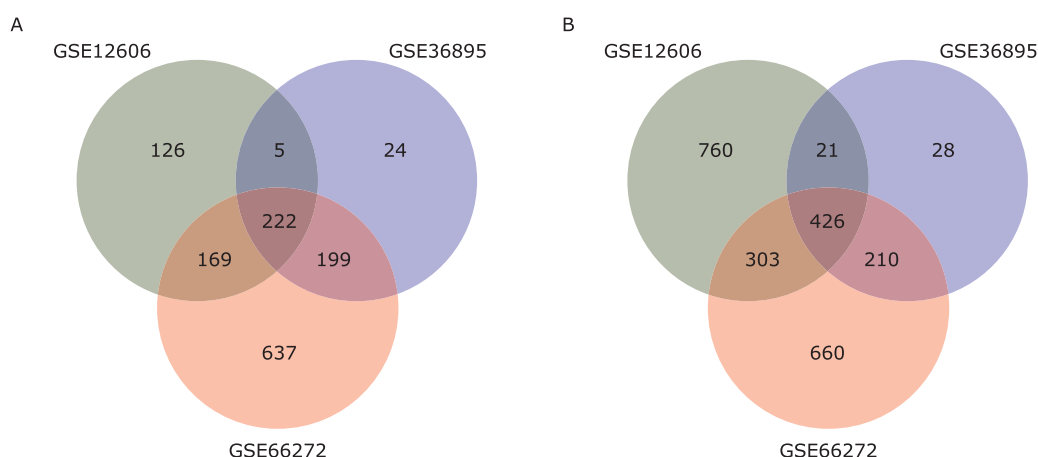


Figure 1. The Venn diagram of 648 commonly differentially expressed genes (c-DEGs) in the three datasets. A. 222 up-regulated c-DEGs ($\log_{2}FC > 1.5$); B. 426 down-regulated c-DEGs ($\log_{2}FC < -1.5$).

c-DEGs were particularly enriched in hypoxia inducible factor-1 (HIF-1) signaling pathway and phagosome, and down-regulated were significantly enriched in metabolic pathways (**Fig. 3**).

The Function DEGs may fulfil in ccRCC

We used STRING website and Cytoscape software to structure a PPI network complex which composed of 549 nodes and 2571 edges, but the PPI network of c-DEGs lost 99 nodes. Next, we applied Cytotype MCODE to identify the core nodes of the c-DEGs PPI network and found 28 core genes (*ANLN*, *ASPM*, *BIRC5*, *BUB1*, *CCNB2*, *CCNE2*, *CDC6*, *CDCA2*, *CDCA7*, *CDK1*, *CENPK*,

CENPU, *CEP55*, *DLGAP5*, *DTL*, *KIAA0101*, *KIF14*, *KIF20A*, *NUF2*, *NUSAP1*, *PRC1*, *PTTG1*, *RAD51AP1*, *RRM2*, *TOP2A*, *TPX2*, *TTK*, *UHRF1*) consisting of 28 nodes and 361 edges (**Fig. 4**). At last, KEGG pathway enrichment re-analysis showed that 28 nodes were enriched in cell cycle (*CCNE2*, *CDK1*, *CDC6*, *CCNB2*, *BUB1*, *TTK* and *PTTG1*) and p53 signaling pathway (*CCNE2*, *CDK1*, *CCNB2* and *RRM2*), as shown in **Fig. 5**.

DEGs involved in prognosis

We exploited GEPIA Survival Plot to determine poor prognosis related genes among eight core genes enriched by re-KEGG pathway, which selected by re-KEGG

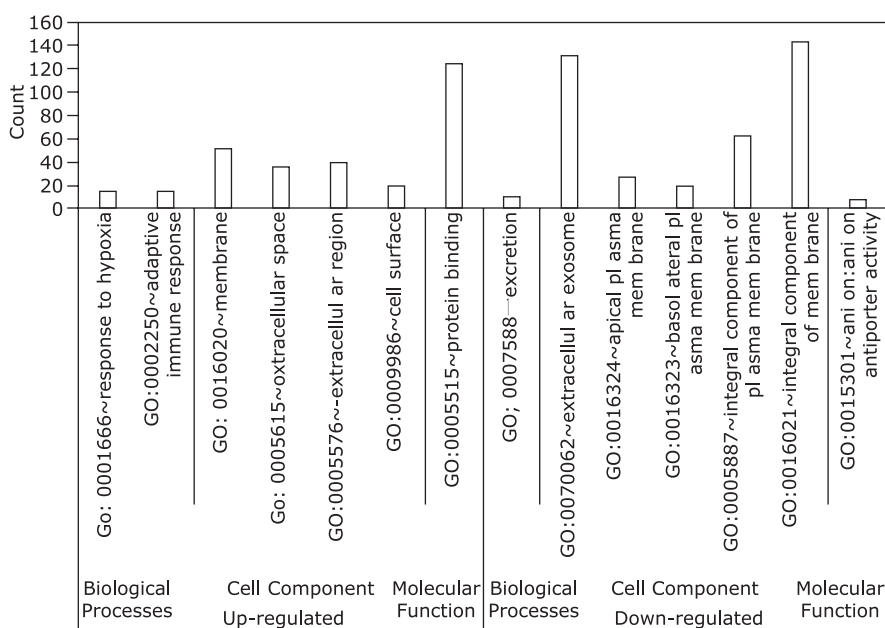


Figure 2. GO analysis showing the biological processes, cell components, and molecular function of clear-cell renal cell carcinoma (ccRCC) that c-DEGs may take part in.

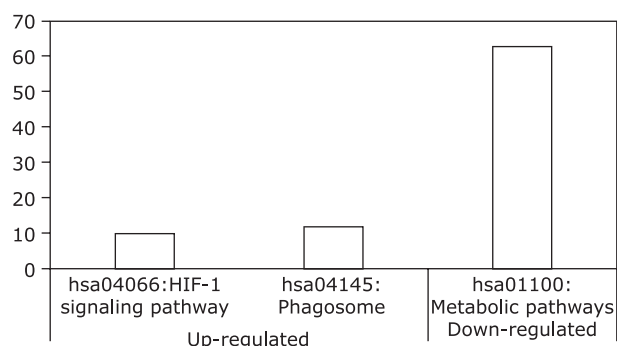


Figure 3. KEGG pathway analysis revealing the function of c-DEGs which can play a role in ccRCC tissues.

pathway enrichment and discovered CDK1, CCNB2, RRM2, BUB1, PTTG1 were significantly related to worse survival and CCNE2, CDC6, TTK were not associated with poor survival (**Fig. 6**). Furthermore, GEPIA Box Plot was used to perform expression analysis of the genes that may have an effect on survival of ccRCC. And then the significant worse survival genes were proceeded expression analysis on box plots of GEPIA and the results showed that BUB1, CCNB2, PTTG1, RRM2 were over expressed in the ccRCC tissues in contrast to the normal tissues ($P < 0.05$, **Fig. 7**).

DISCUSSION

The ccRCC is a malignant tumor that originates

from the urinary tubular epithelial system of renal parenchyma, and it accounts for 60%-85% of the renal cell carcinoma.^[7, 8] Because of accumulating glycogen and lipid in position of ccRCC cells, it is not sensitive to radio- or chemo-therapy.^[9] Fortunately, molecular targeted therapy for ccRCC has made certain progress, and 20%-40% ccRCC patients have been effectively treated. However, molecular targeted therapy for high-risk ccRCC patients is not effective, and the long-term survival rate is not satisfactory.^[10, 11] Therefore, we decided to compare the expression pattern of ccRCC tissues and normal tissues through data mining to investigate the commonly differentially expressed and prognosis related genes in order to reveal the underlying mechanisms.

In this study, we utilized bioinformatic analysis to analyze the selected datasets GSE12606, GSE36895 and GSE66272 and identified four up-regulated genes such as *CCNB2*, *RRM2*, *BUB1*, *PTTG1* in ccRCC tissues that correlated with worse survival of ccRCC.

BUB1 (Budding uninhibited by benzimidazoles-1) gene encodes a mitotic checkpoint serine/threonine kinase which is considered as a sensitive and specific biomarker for gastric cancer, breast cancer, colorectal cancer etc.^[12-15] KEGG pathway re-analysis results showed that BUB1 was involved in cell cycle pathway compactly related to ccRCC pathogenesis. In addition, BUB1 as a key mediator of TGF- β signaling that interacts with TGFBR1 in the presence of TGF- β and

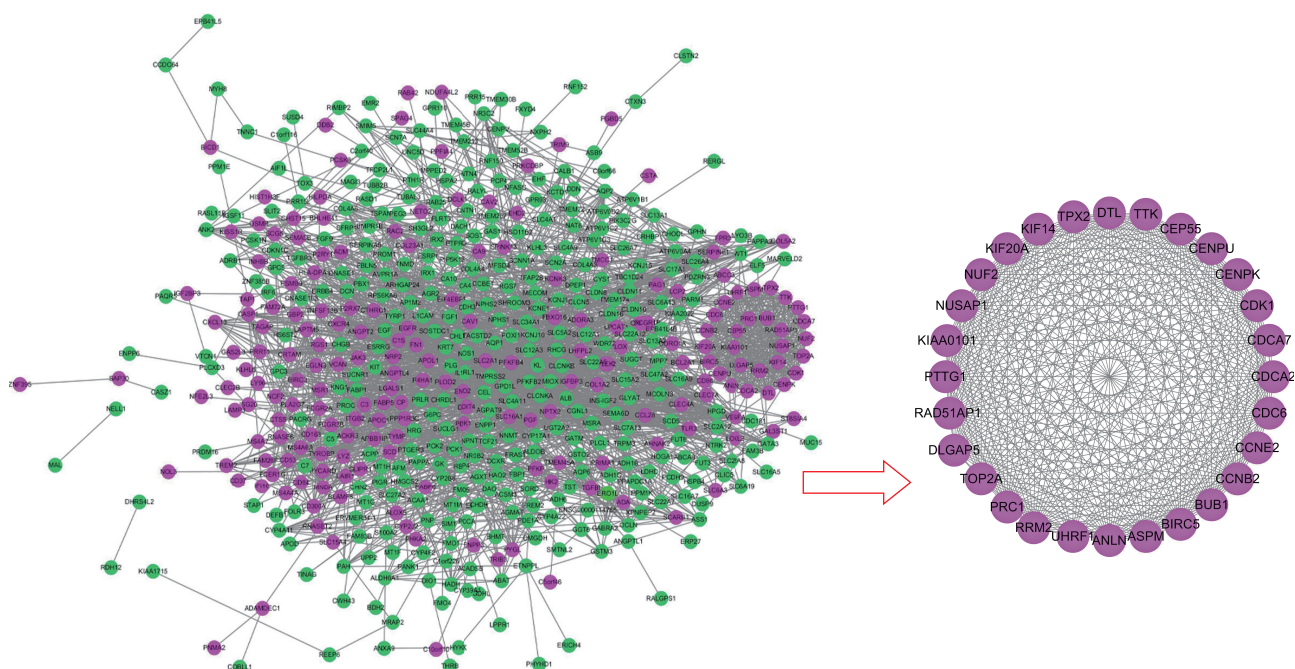
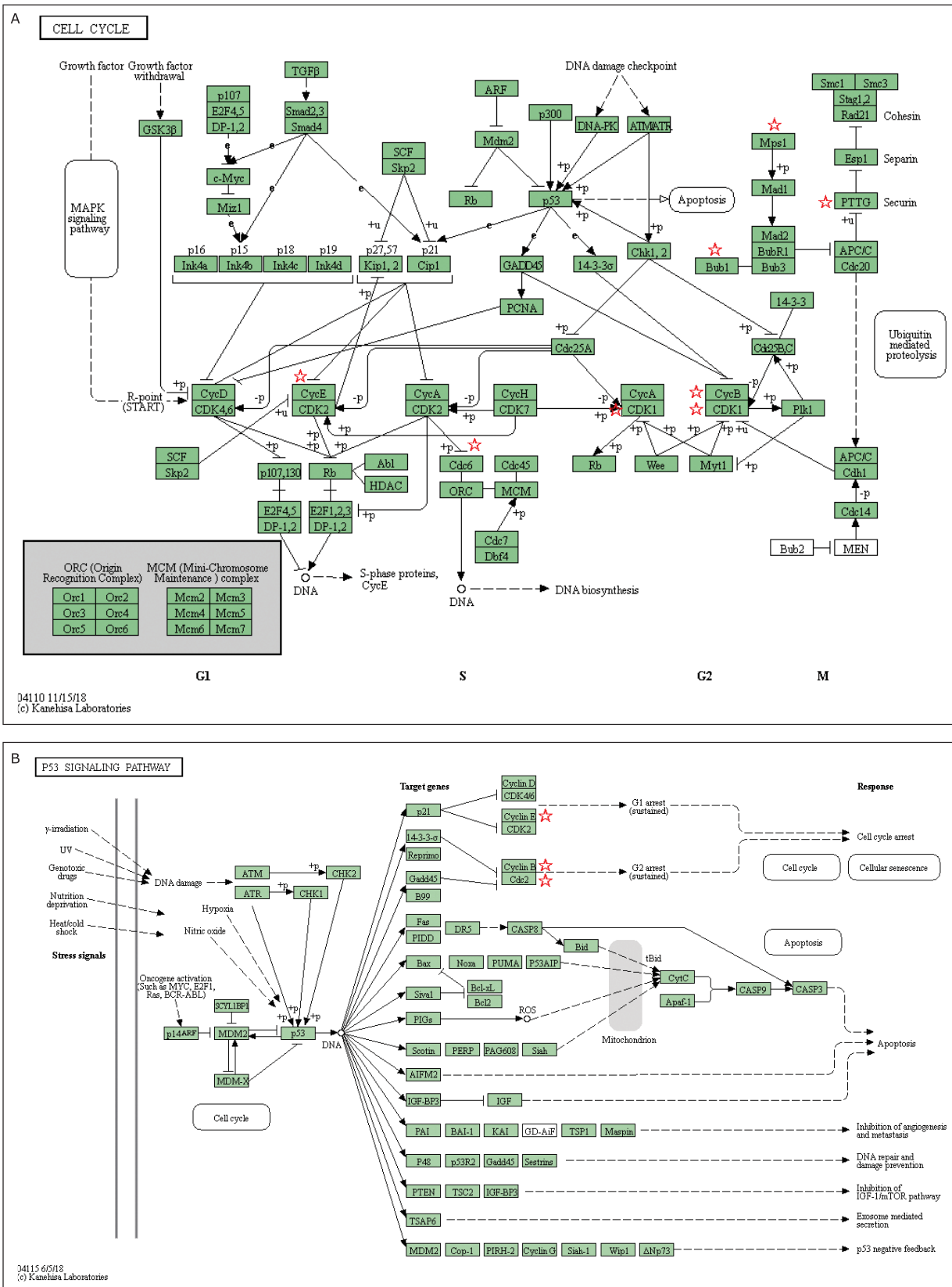


Figure 4. PPI network of c-DEGs structured by STRING and Module analysis. The module consisted of 28 nodes and 361 edges. Purple represents up-regulated genes and green indicates down-regulated genes.



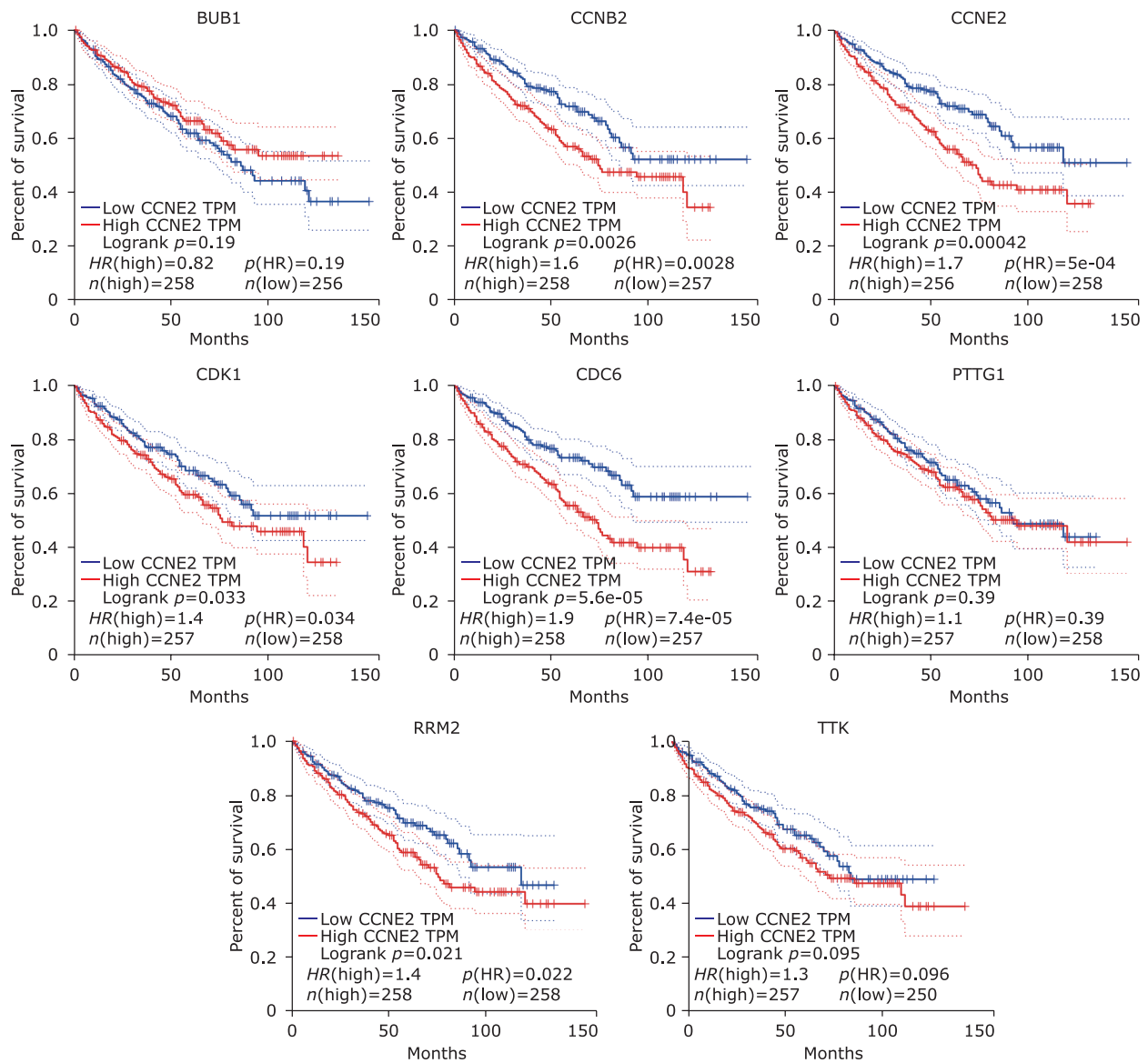


Figure 6. The genes that participate in worse survival of ccRCC.

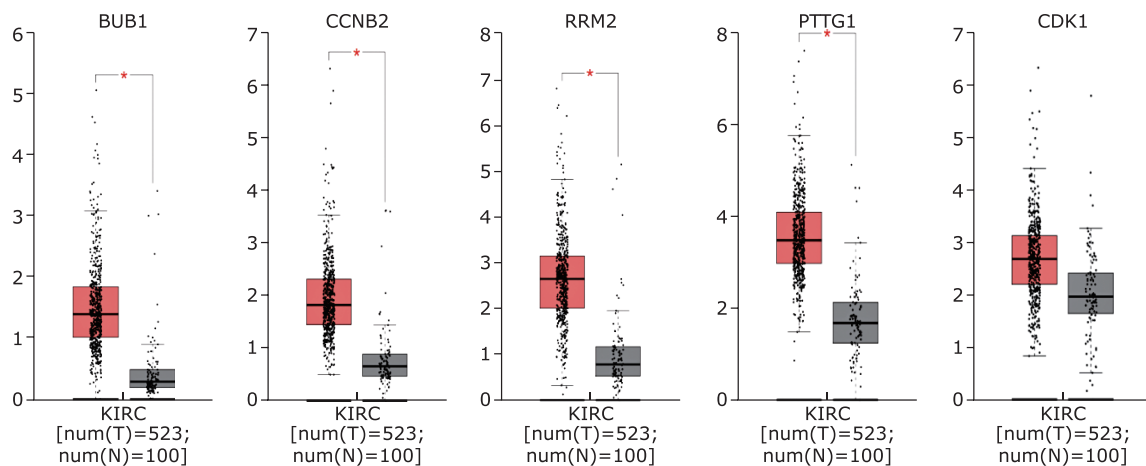


Figure 7. Expression levels of five poor prognosis related genes in ccRCC patients compared to healthy people. Red color means tumor tissues and grey color indicates normal tissues.

promotes the heterodimerization of TGFBR1 and TGFBR2, opened the growth of invasive cancer cells.^[16, 17] In subsequent experiments, it was found that in various normal tissues and cancers, small molecule inhibitors of BUB1 kinase activity (2OH-BNPP1) and kinase-deficient mutants of BUB1 inhibited formation of TGF- β and ternary complexes. Administration of 2OH-BNPP1 to mice bearing lung carcinoma xenografts reduced the amount of phosphorylated SMAD2 in tumor tissue.^[17] These studies suggest that BUB1 can regulate prognosis of cancer by regulating TGF- β signaling. Combining our survival analysis, we infer that *BUB1* may be an indicator for diagnosis and prognosis of ccRCC.

CCNB2 (cyclin B2) which is a member of cyclin family proteins, regulates the activities of cyclin dependent kinases (CDKs). Different cyclins function spatially and temporally in specific phases of cell cycle^[18, 19] and its expression is increased in a variety of human cancers, such as colorectal adenocarcinoma and gastric cancer, etc.^[20, 21] Mo *et al.*^[22] found that serous *CCNB2* mRNA expression was increased in cancer patients and associated with cancer stage and metastasis. After therapeutic treatment, its expression level was significantly decreased compared with prior treatment. In order to explore the relationship between *CCNB2* and renal cell cancer, Yamamura *et al.*^[23] discovered that the *CCNB2* gene was significantly increased in stably expressed sFRP2 renal cell lines compared with A498 renal cancer cell lines. Although there is no more evidence that *CCNB2* is closely linked to ccRCC, the cyclin family proteins play an important role in the diagnosis, prognosis and treatment of ccRCC patients and associate with cell cycle.^[24, 25] And the molecular mechanism of *CCNB2* in ccRCC awaits further investigation.

PTTG1 (pituitary tumor-transforming gene-1) is a recently identified oncogene involved in the progression of malignant tumors, and it was first isolated from rat pituitary tumor cells in 1997.^[26, 27] In contrast to its restricted expression in normal tissues, *PTTG1* is largely examined in various cancers and is adjoined with metastasis and poor clinical outcome.^[28, 29] Wei *et al.*^[26] demonstrated that *PTTG1* mRNA and protein levels were significantly higher in ccRCC than normal tissues and its expression was significantly correlated with T stage, N classification, metastasis, recurrence and Fuhrman grade, which suggest that the *PTTG1* over expression indicates a poor prognosis of ccRCC patients. And the other target gene is *RRM2* (ribonucleotide reductase subunit M2) which encodes an essential protein for DNA

synthesis and is responsible for the reduction of ribonucleotides to deoxyribonucleotides, providing a balanced supply of precursors for DNA synthesis and repair.^[30] Morikawa *et al.*^[31] found that the *RRM2* siRNA inhibited the cell proliferation, migration and invasion and cell apoptosis was increased in primary ccRCC cell lines, indicating that *RRM2* inhibitor may be used as an important potential target drug in the treatment of ccRCC.

In conclusion, we have identified several significant prognostic factors in ccRCC patients using integrated bioinformatic analysis. We have identified commonly changed 648 c-DEGs candidate genes, and finally found 4 mostly changed genes (*BUB1*, *CCNB2*, *PTTG1*, *RRM2*), which were significant enriched in cell cycle and p53 signaling pathway. These findings could provide useful biomarkers related to survival and some effective target for ccRCC treatment.

Conflicts of Interest Statement

The authors declare no conflict of interests.

REFERENCES

1. Li P, Znaor A, Holcatova I, et al. Regional geographic variations in kidney cancer incidence rates in European countries. *Eur Urol* 2015; 67(6):1134-41. doi: 10.1016/j.eururo.2014.11.001.
2. Srinivasan R, Ricketts CJ, Sourbier C, et al. New strategies in renal cell carcinoma: targeting the genetic and metabolic basis of disease. *Clin Cancer Res* 2015; 21(1):10-7. doi: 10.1158/1078-0432.CCR-13-2993.
3. Siegel R, Naishadham D and Jemal A. Cancer statistics. *CA Cancer J Clin* 2013; 63(1):11-30. doi: 10.3322/caac.21166.
4. Capitanio U and Montorsi F. Renal cancer. *Lancet* 2016; 387(10021):894-906. doi: 10.1016/S0140-6736(15)00046-X.
5. Vogelstein B, Papadopoulos N, Velculescu VE, et al. Cancer genome landscapes. *Science* 2013; 339(6127):1546-58. doi: 10.1126/science.1235122.
6. Feng H, Gu ZY, Li Q, et al. Identification of significant genes with poor prognosis in ovarian cancer via bioinformatical analysis. *J Ovarian Res* 2019; 12(1):35. doi: 10.1186/s13048-019-0508-2.
7. Na YQ, Ye ZQ, Sun YH, et al. Diagnosis and treatment of renal cell carcinoma guide manual. In: Xiao J, Yand F, editors. The Chinese department of urology disease diagnosis and treatment guide manual, 2014 ed. Beijing: People Health Publishing House, 2013. p. 1-29.
8. Li DY, Song YS. Comparison of clinical data of renal

- cell carcinoma between elderly and middle aged and young patients. *J Modern Oncology* 2017; 25(5):740-3. doi: 10.3969/j. issn.1672-4992.2017.05.018.
9. Linehan WM, Walther MM, Zbar B. The genetic basis of cancer of the kidney. *J Urol* 2003; 170(6 pt 1):2163-72. doi: 10.1097/01.ju.0000096060.92 397.ed.
 10. Duensing S, Hohenfellner M. Adjuvant therapy for renal cell carcinoma: settled for now. *Lancet* 2016; 387(10032):1973-4. doi: 10.1016/S0140-6736(16)00653-X.
 11. Krabbe LM, Bagrodia A, Margnlis V, et al. Surgical management of renal cell carcinoma. *Semin Intervent Radiol* 2014; 31(1):27-32. doi: 10.1055/s-0033-1363840.
 12. Kim HS, Park KH, Sun AK, et al. Frequent mutations of human Mad2, but not Bub1, in gastric cancers cause defective mitotic spindle checkpoint. *Mutat Res* 2005; 578(1-2):187-201. doi: 10.1016/j. mrfm-mm.2005.05.020.
 13. Mur P, De Voer RM, Olivera-Salguero R, et al. Germline mutations in the spindle assembly checkpoint genes BUB1 and BUB3 are infrequent in familial colorectal cancer and polyposis. *Mol Cancer* 2018; 17(1):23. doi: 10.1186/s12943-018-0762-8.
 14. Myrie KA, Percy MJ, Azim JN, et al. Mutation and expression analysis of human BUB1 and BUB1B in aneuploid breast cancer cell lines. *Cancer Lett* 2000; 152(2):193-9. doi: 10.1016/s0304-3835(00)00340-2.
 15. Burum-Auensen E, Deangelis PM, Schjølberg AR, et al. Spindle proteins Aurora A and BUB1B, but not Mad2, are aberrantly expressed in dysplastic mucosa of patients with longstanding ulcerative colitis. *J Clin Pathol* 2017; 60(12):1403-8. doi: 10.1136/jcp.2006.044305.
 16. Moustakas A. The mitotic checkpoint protein kinase BUB1 is an engine in the TGF- β signaling apparatus. *Sci Signal* 2015; 8(359):fs1. doi: 10.1126/scisignal.aaa4636.
 17. Nyati S, Schinske-sebolt K, Pitchiaya S, et al. The kinase activity of the Ser/Thr kinase BUB1 promotes TGF- β signaling. *Sci Signal* 2015; 8(358):ra1. doi: 10.1126/scisignal.2005379.
 18. Qian XT, Song XK, He Y, et al. CCNB2 overexpression is a poor prognostic biomarker in Chinese NSCLC patients. *Biomed Pharmacother* 2015; 74:222-7. doi: 10.1016/j.biopha.2015.08.004.
 19. Vermeulen K, Bockstaele DRV, Berneman ZN. The cell cycle: a review of regulation, deregulation and therapeutic targets in cancer. *Cell Prolif* 2003; 36(3):131-49. doi: 10.1046/j.1365-2184.2003.00266.x.
 20. Park SH, Yu GR, Kim WH, et al. NF-Y-dependent cyclin B2 expression in colorectal adenocarcinoma. *Clin Cancer Res* 2007; 13(3):858-67. doi: 10.1158/1078-0432.CCR-06-1461.
 21. Wang DG, Chen G, Wen XY, et al. Identification of biomarkers for diagnosis of gastric cancer by bioinformatics. *Asian Pac J Cancer Prev* 2015; 16(4):1361-5. doi: 10.7314/apjcp.2015.16.4.1361.
 22. Mo ML, Chen Z, Li J, et al. Use of serum circulating Ccnb2 in cancer surveillance. *Int J Biol Markers* 2010; 25(4):236-42. doi: 10.5301/JBM.2010.6088.
 23. Yamamura S, Kawakami K, Hirata H, et al. Oncogenic functions of secreted frizzled-related protein 2 in human renal cancer. *Mol Cancer Ther* 2010; 9(6):1680-7. doi: 10.1158/1535-7163.MCT-10-0012.
 24. Hong Y, Huang X, An L, et al. Overexpression of COPS3 promotes clear cell renal cell carcinoma progression via regulation of phospho-AKT (Thr308), cyclin D1 and caspase-3. *Exp Cell Res* 2018; 365(2):163-70. doi: 10.1016/j.yexcr.2018.02.025.
 25. Haddad AQ, Luo JH, Krabbe LM, et al. Prognostic value of tissue-based biomarker signature in clear cell renal cell carcinoma. *BJU Int* 2017; 119(5):741-7. doi: 10.1111/bju.13776.
 26. Wei C, Yang XL, Xi JH, et al. High expression of pituitary tumor-transforming gene-1 predicts poor prognosis in clear cell renal cell carcinoma. *Mol Clin Oncol* 2015; 3(2):387-91. doi: 10.3892/mco.2014.478.
 27. Pei L, Melmed S. Isolation and characterization of a pituitary tumor-transforming gene (PTTG). *Mol Endocrinol* 1997; 11(4):433-41. doi: 10.1210/mend.11.4.9911.
 28. Feng ZZ, Chen JW, Yang ZR, et al. Expression of PTTG1 and PTEN in endometrial carcinoma: correlation with tumorigenesis and progression. *Med Oncol* 2012; 29(1):304-10. doi: 10.1007/s12032-010-9775-x.
 29. Yoon CH, Kim MJ, Lee H, et al. PTTG1 oncogene promotes tumor malignancy via epithelial to mesenchymal transition and expansion of cancer stem cell population. *J Biol Chem* 2012; 287(23):19516-27. doi: 10.1074/jbc.M111.337428.
 30. Rahman MA, Amin ARM, Wang X, et al. Systemic delivery of siRNA nanoparticles targeting RRM2 suppresses head and neck tumor growth. *J Control Release* 2012; 159(3):384-92. doi: 10.1016/j.jconrel.2012.01.045.
 31. Morikawa T, Hino R, Uozaki H, et al. Expression of ribonucleotide reductase M2 subunit in gastric cancer and effects of RRM2 inhibition *in vitro*. *Hum Pathol* 2010; 41(12):1742-8. doi: 10.1016/j.humpath.2010.06.001.

论著

垂体瘤切除术后突发感音神经性聋—病例系列报告及文献复习

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摘要

目的 经蝶垂体瘤术后患者较少出现延迟的突发性感音神经性聋。本研究报告了3例垂体瘤患者, 术后无脑脊液漏或脑膜炎, 但是在术后3至7日发生突发性感音神经性聋, 并讨论了可能的致聋原因。

方法 对3例经蝶垂体瘤术后延迟出现突发性感音神经性聋病例, 报告其病史、突发性聋的发生时间、伴随症状如头痛、耳鸣、眩晕、耳闷等, 以及术后MRI表现、治疗、听力恢复等情况。

结果 术后3至7日突发极重度感音神经性聋的3例患者, 听力下降前全都伴发头痛、耳鸣、眩晕。1例有间断反复发作的眩晕、耳闷、波动性听力下降, 持续至术后1个月。2例有动脉硬化、冠心病史或脑梗史。3例患者中2例术后第1天MRI显示梗阻性脑积水。在口服泼尼松、鼓室注射低塞米松、服用神经营养药物和扩血管药物3至8个月之后, 3例患者听力均有部分恢复。术后梗阻性脑积水和内听动脉缺血可能造成术后耳聋。

结论 经蝶垂体瘤术后梗阻性脑积水和迷路动脉缺血可能引起延迟出现的突发性感音神经性聋。

关键词: 经蝶垂体瘤切除术; 阻塞性脑积水; 内听动脉缺血; 突发性感音神经性聋; 耳鸣

中文摘要

基于生物信息学分析肾透明细胞癌预后相关关键基因

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摘要

目的 识别与肾透明细胞癌预后相关的关键基因。

方法 基于生物信息学分析技术对GEO数据库中的62个肾透明细胞癌样本和54个正常肾组织的数据集(GSE12606, GSE36895和GSE66272)进行分析。首先在GEO2R和J Venn网站上获取差异表达基因, 之后采用GO和KEGG对基因进行功能注释; 在使用STRING网站构建PPI网络后, 采用Cytoscape软件的MCODE App对核心基因进行筛选; 最后利用GEPIA网站分析与生存率有关的核心基因。

结果 我们共发现648个差异表达基因, 包括222个上调表达基因和426个下调表达基因。PPI蛋白网络分析共发现28个表达上调的核心基因, 其中7个核心基因(*CCNE2*, *CDK1*, *CDC6*, *CCNB2*, *BUB1*, *TTK*和*PTTG1*)富集于细胞周期, 4个(*CCNE2*, *CDK1*, *CCNB2*和*RRM2*)富集于p53信号通路。GEPIA生存率分析发现:*CDK1*, *CCNB2*, *RRM2*, *BUB1*, *PTTG1*与肾透明细胞癌患者的生存率密切相关。肾透明细胞癌患者*BUB1*, *CCNB2*, *PTTG1*和*RRM2*等4个关键基因的表达式量高于正常人群($P<0.05$)。

结论 *BUB1*、*CCNB2*、*PTTG1*、*RRM2*等4个上调差异表达基因可能是肾透明细胞癌患者预后关键预测基因。

关键词: 肾透明细胞癌; 生物信息学分析; 差异表达基因