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Genetic Analysis Identifies the Role of *HLF* in Renal Cell Carcinoma

CHAO-YUAN HUANG[1*], SHU-PIN HUANG[2,3,4,5*], YU-MEI HSUEH[6,7*], LIH-CHYANG CHEN[8], TE-LING LU[9] and BO-YING BAO[9,10,11]

[1]*Department of Urology, National Taiwan University Hospital, College of Medicine, National Taiwan University, Taipei, Taiwan, R.O.C.;*
[2]*Department of Urology, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan, R.O.C.;*
[3]*Graduate Institute of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan, R.O.C.;*
[4]*Department of Urology, Faculty of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan, R.O.C.;*
[5]*Center for Cancer Research, Kaohsiung Medical University, Kaohsiung, Taiwan, R.O.C.;*
[6]*Department of Family Medicine, Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan, R.O.C.;*
[7]*Department of Public Health, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan, R.O.C.;*
[8]*Department of Medicine, Mackay Medical College, New Taipei City, Taiwan, R.O.C.;*
[9]*Department of Pharmacy, China Medical University, Taichung, Taiwan, R.O.C.;*
[10]*Sex Hormone Research Center, China Medical University Hospital, Taichung, Taiwan, R.O.C.;*
[11]*Department of Nursing, Asia University, Taichung, Taiwan, R.O.C.*

Abstract. *Background/Aim: Circadian rhythm is an internal clock that regulates the cycles of many biological functions. Epidemiological studies have linked aberrant circadian rhythm to an increased susceptibility to cancer and poor patient prognosis. However, there remains a gap in our understanding of genetic variants related to the circadian pathway in renal cell carcinoma (RCC) progression. Patients and Methods: We examined the associations of 150 single nucleotide polymorphisms (SNPs) in 12 core circadian pathway genes with RCC risk and survival in 630 patients with RCC and controls. Results: After adjusting for multiple comparisons and performing multivariate analyses, we found that the HLF rs6504958 polymorphism was significantly associated with RCC risk (q<0.05), whereas, no SNP association was significant for survival. Furthermore, the rs6504958 G allele was associated with reduced expression of HLF; consequently, a lower HLF expression was correlated with more advanced RCC. Moreover, a meta-analysis of six kidney cancer gene expression datasets demonstrated that an elevated HLF expression was associated with a favorable prognosis in patients with RCC (hazard ratio=0.70, 95% confidence interval=0.65-0.76, p<0.001). Conclusion: These findings implicate the potential protective role of HLF in the progression of RCC.*

*These Authors contributed equally to this work.

Correspondence to: Bo-Ying Bao, Department of Pharmacy, China Medical University, 91 Hsueh-Shih Road, Taichung 404, Taiwan, R.O.C. Tel.: +886 422053366 ext. 5126, Fax: +886 422031075, e-mail: bao@mail.cmu.edu.tw

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It was estimated that 403,262 new cases of kidney cancer were diagnosed and 175,098 people died from the disease worldwide in 2018 (1). Multiple lifestyle, environmental and genetic risk factors have been reported to contribute to kidney carcinogenesis. Moreover, the Nordic Twin Study of Cancer identified kidney cancer as a highly heritable cancer with a 38% estimate of heritability (2). Renal cell carcinoma (RCC), derived from the renal epithelium, accounts for 80-85% of all kidney cancer (3). Recent meta-analyses of genome-wide association studies have identified 13 risky loci in von Hippel–Lindau/β-catenin signaling, telomere maintenance, and brahma-related gene 1/brahma-associated factor (BAF)/polybromo-associated BAF epigenetic pathways as putative drivers of RCC (4). However, these risky loci represent only approximately 10% of the familial risk of RCC (4), suggesting that there remain considerable undetermined genetic factors influencing the risk of RCC.

Recent studies have linked circadian dysfunction to an increased susceptibility in different types of cancer, including lung, breast, prostate, colorectal, liver, and non-Hodgkin lymphoma (5-10). In fact, the International Agency for Research on Cancer of the World Health Organization has suggested that shift-work that involves circadian disruption is probably carcinogenic to humans. The circadian rhythms are generated *via* a complex auto-regulatory network of 'clock' genes; these genes regulate physiological and behavioral activities to adapt to periodic environmental changes. The molecular circadian clock is regulated by the transcription–translation feedback loops that are driven by the heterodimers of aryl hydrocarbon receptor nuclear translocator-like (ARNTL)/clock circadian regulator (CLOCK) and ARNTL/neuronal PAS domain protein 2 (NPAS2). These heterodimers transcriptionally activate the downstream clock-controlled genes, period (*PER1-3*) and cryptochrome (*CRY1-2*), during the day. The PER and CRY proteins form a heterodimer, which is translocated to the nucleus and act on the ARNTL/CLOCK/NPAS2 complexes to repress their own transcription during the night. PER and CRY proteins are then phosphorylated by casein kinase 1 epsilon (CSNK1E) and degraded to initiate a new circadian cycle with a periodicity of around 24 hours (11). Many clock-dependent transcription factors such as hepatic leukemia factor (HLF), thyrotrophic embryonic factor, and albumin D-site-binding protein (DBP) help circadian adjustment in neurotransmitter metabolism (12), xenobiotic detoxification (13), immune homeostasis (14), and renal function (15). Furthermore, molecular epidemiology studies on the relationship between circadian gene polymorphisms and cancer susceptibility have demonstrated that variants in several circadian genes are frequently associated with human cancer, such as *ARNTL* gene variants in prostate (16), breast (17), and ovarian (18) cancer. However, to date, no study has investigated the relationship between circadian gene variants and RCC. Therefore, we conducted an association study to comprehensively evaluate the role of genetic variants in the circadian pathway in the risk and survival of patients with RCC.

Patients and Methods

Study population and participant data collection. This study recruited 312 patients with pathologically proven RCC and 318 age- and gender-matched healthy controls with no evidence of malignancy from three Taipei city hospitals: Taipei Municipal Wan Fang Hospital, Taipei Medical University Hospital, and National Taiwan University Hospital (19, 20). The participants' demographic and clinical information were collected through in-person interviews and medical records, respectively. The median follow-up period for the patients was 84.6 months. During the study period, metastasis-free survival was defined as the interval from diagnosis to the detection of a distant metastasis, while overall survival was defined as the interval from diagnosis to death. This study was approved by the Research Ethics Committee of National Taiwan University Hospital (9100201527) and was carried out in accordance with the Declaration of Helsinki. All participants gave their written informed consent before blood sample collection.

Table I. *The clinical characteristics of the study population*.

Characteristic	Cases (n=312)	Controls (n=318)	*p*-Value
Age, years			
Median (IQR)	57 (48-68)	57 (47-68)	0.964
Gender, n (%)			
Male	209 (67.0)	210 (66.0)	0.801
Female	103 (33.0)	108 (34.0)	
BMI, kg/m^2			
Median (IQR)	24.4 (22.3-27.6)	24.6 (22.6-26.7)	0.561
Cigarette smoking status, n (%)			
Never	198 (63.5)	213 (67.0)	0.354
Ever	114 (36.5)	105 (33.0)	
Alcohol consumption, n (%)			
Never	236 (75.6)	183 (57.5)	**<0.001**
Ever	76 (24.4)	135 (42.5)	
Hypertension, n (%)			
No	177 (56.9)	235 (75.1)	**<0.001**
Yes	134 (43.1)	78 (24.9)	
Diabetes, n (%)			
No	249 (80.1)	296 (93.7)	**<0.001**
Yes	62 (19.9)	20 (6.3)	
Stage, n (%)			
I-II	240 (81.4)		
III-IV	55 (18.6)		
Grade, n (%)			
I-II	206 (75.2)		
III-IV	68 (24.8)		
Follow-up[a], n (%)			
Metastasis	55 (17.6)		
Deaths	34 (10.9)		

IQR: Interquartile range; BMI: body mass index. [a]With median follow-up of 84.6 months. Statistically significant *p*-values are shown in bold.

Single nucleotide polymorphism (SNP) selection and genotyping. Haplotype-tagging SNPs were selected from within 10-kb flanking regions of the 12 circadian pathway genes from the Han Chinese data in the 1000 Genomes Project as per previous studies (21, 22). The genomic DNA was extracted from the peripheral blood of each participant and then genotyped using Affymetrix Axiom Genotyping arrays at the National Centre for Genome Medicine, Taiwan (23). Quality control was performed to remove SNPs with call rates <0.95, minor allelic frequencies <0.03, and Hardy–Weinberg equilibrium <0.001. A total of 150 SNPs remained for further analyses.

Bioinformatic analyses. HaploReg v4.1 was used to annotate the identified SNPs to evaluate their functional significance (24). The Genotype-Tissue Expression (GTEx) portal was used to evaluate the SNP–gene expression quantitative trait loci associations (25). Finally, six public kidney cancer gene expression datasets from the

Table II. *The association between genotype of hepatic leukemia factor single nucleotide polymorphism rs6504958 and renal cell carcinoma risk.*

Genotype	Cases, n (%)	Controls, n (%)	OR (95% CI)	*p*-Value	*q*	OR (95% CI)[a]	*p*-Value[a]
GG	91 (29.2)	60 (18.9)	1.00			1.00	
GT	161 (51.6)	167 (52.5)	0.64 (0.43-0.94)	**0.023**		0.61 (0.39-0.93)	**0.023**
TT	60 (19.2)	91 (28.6)	0.44 (0.27-0.69)	**0.000397**		0.42 (0.26-0.70)	**0.001**
Trend			0.66 (0.52-0.83)	**0.000397**	0.050	0.65 (0.51-0.84)	**0.001**

CI: Confidence interval; OR: odds ratio. [a]ORs were adjusted for age, gender, body mass index, cigarette smoking status, alcohol consumption, and history of hypertension and diabetes. Statistically significant *p*-values are shown in bold.

Gene Expression Omnibus and The Cancer Genome Atlas (TCGA) were used to evaluate the relation between gene expression and patient prognosis (26-29).

Statistical analyses. The patient characteristics are presented as numbers or percentages for categorical variables and as medians or interquartile ranges for the continuous variables. These variables were compared between the patients with RCC and healthy controls using the chi-square test or Mann–Whitney *U*-test. Then to assess the association between the SNPs and clinical outcomes, a logistic regression analysis was used for the dichotomous data and a Cox regression analysis for the time-to-event variables. Next, Spearman's correlation was used to examine the association between *HLF* expression and the clinicopathological characteristics of RCC. Finally, Kaplan–Meier survival curves were plotted and log-rank tests were conducted to evaluate the differences in survival time according to the *HLF* expression. These statistical analyses were performed using Statistical Package for the Social Sciences (version 19.0.0; IBM, Armonk, NY, USA) and the significance was defined as $p<0.05$. A false-discovery rate (q value) was computed to adjust for multiple comparisons (30).

Results

Study participant characteristics. The demographic and clinical characteristics of 312 patients with RCC and 318 healthy controls are presented in Table I. There was no difference observed in the age, gender, body mass index, and cigarette smoking status between the patients and controls. However, the patients had lower alcohol consumption and a higher prevalence of hypertension and diabetes ($p<0.001$). Moreover, the majority of the patients had stage I-II (81.4%) and grade I-II (75.2%) tumors. Furthermore, 55 (17.6%) patients developed metastasis and 34 (10.9%) died during the follow-up period.

Associations between the circadian pathway genetic variants and RCC risk. The associations between the circadian pathway genetic variants and RCC risk are presented in Supplementary Table I (https://drive.google.com/file/d/1TgGShleXQqyPEJba5YvG5ylyVqE-4CQg/view). Of the 150 SNPs, a total of 10 SNPs from four genes: *PER3*, *ARNTL*, *HLF* and *DBP*, showed suggestive associations ($p<0.05$) with the risk of RCC; after adjusting for multiple comparisons, only *HLF* rs6504958 polymorphism remained significant ($q<0.05$). The *HLF* rs6504958 T allele was also associated with a reduced RCC risk in a dose–response manner [odds ratio (OR)=0.66, 95% confidence interval (CI)=0.52-0.83, $p=0.000397$; Table II]. The multivariate analysis (after adjusting for age, gender, body mass index, cigarette smoking status, alcohol consumption, and histories of hypertension and diabetes) further confirmed the association between *HLF* rs6504958 polymorphism and RCC risk (adjusted OR=0.65, 95% CI=0.51-0.84, $p=0.001$; Table II).

Association of circadian-related SNPs with survival in patients with RCC. Next, we evaluated the association of the circadian-related SNPs with metastasis-free survival and overall survival in the patients with RCC (Supplementary Table I). Six SNPs from *PER3*, *NPAS2*, *CRY2* and *CSNK1E*, and 14 SNPs from *PER3*, *PER2*, *HLF* and *CSNK1E*, showed nominal associations ($p<0.05$) with metastasis-free survival and overall survival, respectively. However, none of these associations were significant after adjusting for multiple comparisons ($q>0.05$).

Functional analyses of HLF rs6504958 polymorphism. HaploReg identified that rs6504958 polymorphism was located in the promoter histone marks, enhancer histone marks, and DNase hypersensitive sites; it was predicted to alter the regulatory binding motifs as well (Supplementary Table II, https://drive.google.com/file/d/1TgGShleXQqyPEJba5YvG5ylyVqE-4CQg/view). The GTEx data showed that rs6504958 was a direct expression quantitative trait locus that regulated the expression of *HLF*. Furthermore, the rs6504958 G allele was associated with reduced *HLF* expression (Figure 1A) and this down-regulation of *HLF* expression was found in late-stage and high-grade tumors present in TCGA kidney renal clear cell carcinoma (KIRC) dataset (Figure 1B-D). Furthermore, low *HLF* expression was associated with shorter progression-free and overall survival in patients with RCC (Figure 1E-F). Finally, the meta-analysis of six gene-expression datasets demonstrated that high *HLF* expression was associated with a favorable prognosis for patients with kidney cancer (hazard ratio=0.70, 95% CI=0.65-0.76, $p<0.001$, Figure 1G). These results indicate the clinical relevance and potential protective role of *HLF* in RCC.

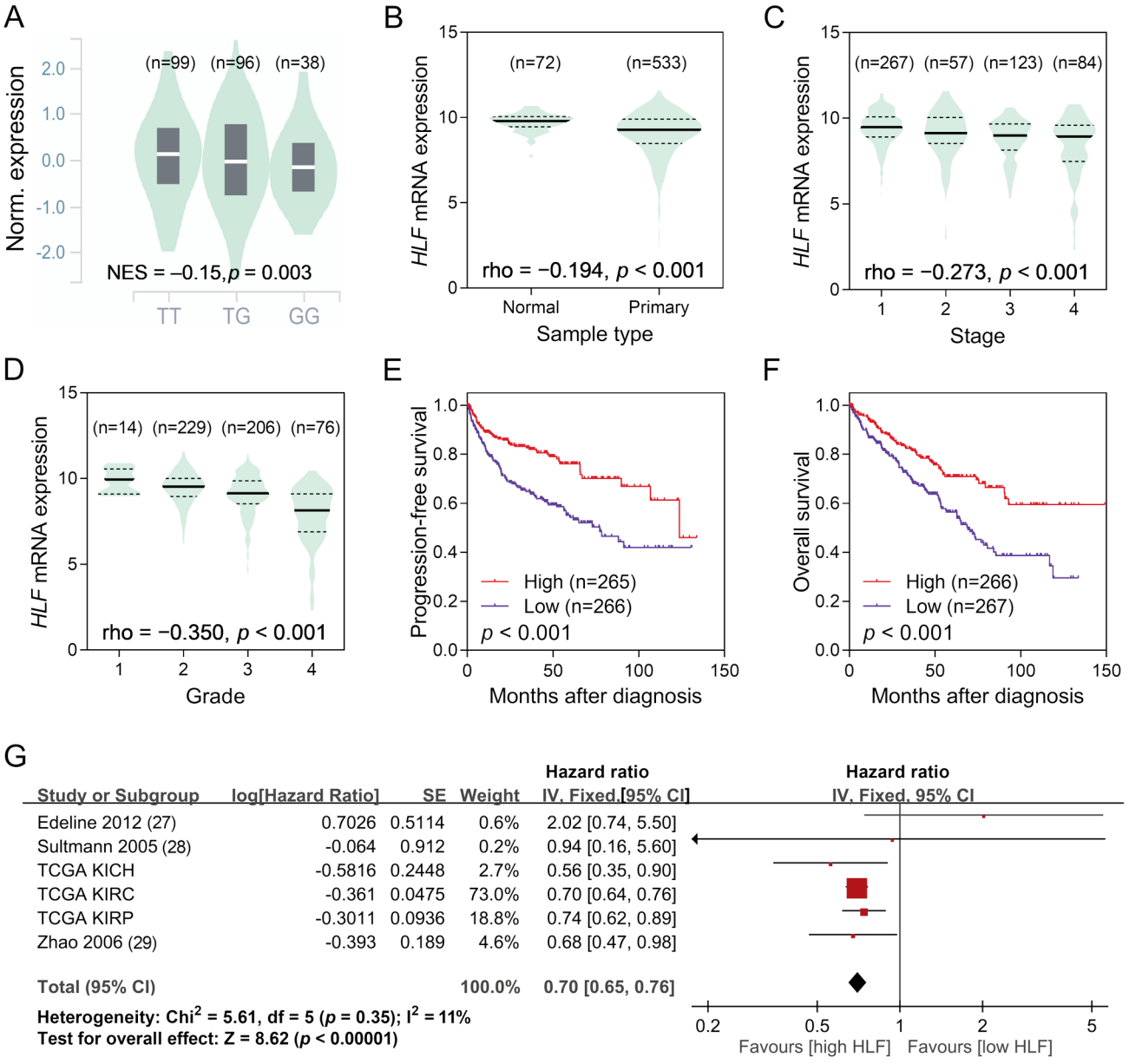

Figure 1. *Functional analyses of hepatic leukemia factor (HLF) rs6504958. A: The effect of rs6504958 genotype (TT, TG, and GG) on HLF expression levels in adrenal gland tissues from the Genotype-Tissue Expression data. HLF expression was shown to be down-regulated in tumor (B), higher stage (C), and higher grade (D) samples. Low expression of HLF was associated with a shorter progression-free (E) and overall (F) survival in The Cancer Genome Atlas (TCGA) kidney renal clear cell carcinoma (KIRC) cohort. G: Meta-analysis of HLF expression and prognosis in patients with kidney cancer. IV: Inverse variance; KIRP: kidney renal papillary cell carcinoma; KICH: kidney chromophobe; NES: normalized effect size; rho: Spearman's rank correlation coefficient; SE: standard error.*

Discussion

In this study, we presented a genetic analysis of circadian-related SNPs in RCC and identified the association of *HLF* rs6504958 polymorphism with RCC risk. Moreover, we demonstrated that rs6504958 affects the *HLF* expression; furthermore, low *HLF* expression is found in more advanced stages of RCC and is correlated with a poorer survival. These observations suggest that *HLF* may play an important role in the progression of RCC.

The SNP rs6504958, located in the intron region of *HLF*, was overlapped with the promoter and enhancer histone

marks, DNase hypersensitivity sites, RNA polymerase II chromatin immunoprecipitation regions, and disrupted the transcription factor binding motifs in various cells. SNPs in these regions may influence gene transcription; consequently, we observed that the *HLF* expression in adrenal gland tissues was associated with the rs6504958 genotype using GTEx data. However, this SNP expression association was not found in the other kidney tissues from the GTEx datasets, possibly due to the small sample sizes. Another *HLF* SNP, rs117137062, was also nominally associated with survival in RCC but this was non-significant after performing multiple comparisons; this was possibly due to a low number of deaths in our study population.

HLF, a member of the proline- and acidic amino acid-rich basic leucine zipper protein family, was initially discovered in aberrant expression of transcription factor E2α–*HLF* fusion gene in early B-lineage acute leukemia, and was found to be expressed in liver and kidney cells (31). Moreover, HLF has been reported to play an important regulatory role in some cancer types. HLF can directly bind to the promoter of *miR-132* and enhance its expression; this in turn inhibits a downstream factor, TTK protein kinase, and suppresses glioma cell proliferation, metastasis, and radio-resistance (32). Our current observations that a high *HLF* expression is correlated with less aggressive tumor characteristics and a favorable patient prognosis are in line with these findings. However, HLF can also transactivate c-JUN to promote tumor initiating cell-like properties of hepatoma cells by reactivating SRY-box transcription factor 2 and POU class 5 homeobox 1 (33). Ectopic HLF expression was shown to increase anchorage-independent growth and inhibit cell death in JB6 mouse epidermal cells (34). These observations raise the possibility that *HLF* may have different roles during tumorigenesis in a tissue- and context-specific manner. Thus, further functional studies are warranted to address the mechanisms underlying *HLF* action in RCC.

Although our study revealed some interesting findings and provided evidence for the relationship between the circadian rhythm and RCC, we must interpret the results with caution due to several inherited limitations of this study. Firstly, a possible selection bias may have occurred because of our hospital-based case–control study design even though the genotypic distribution was in accordance with the Hardy–Weinberg equilibrium. Secondly, our study comprised only Taiwanese participants; hence, our findings may not apply to other ethnicities. Thirdly, the sample size of the current study was relatively small, which may have affected the results. Fourthly, we did not explore the biological mechanisms of *HLF* rs6504958 in regulating the circadian rhythm and its effect on RCC progression. Therefore, more studies with larger sample sizes and inter-ethnic cohorts are needed to confirm our findings.

In summary, our genetic analysis identified a significant association between *HLF* rs6504958 and RCC. Furthermore, we found that rs6504958 influences *HLF* expression and this expression was correlated with the prognosis of RCC. Although our findings require further functional validation, we believe that *HLF* may be a prognostic marker in RCC and may help in a better understanding of RCC pathogenesis.

Conflicts of Interest

The Authors declare that they have no conflicts of interest in regard to this study.

Authors' Contributions

C-YH, S-PH, Y-MH, and B-YB conceptualized and designed the study. C-YH, S-PH, Y-MH, and B-YB performed the experiments. L-CC and T-LL coordinated and supervised data collection. C-YH, S-PH, Y-MH, and B-YB performed the analysis. All the Authors drafted, reviewed and approved the article.

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Supplementary Material

Available at: https://drive.google.com/file/d/1TgGShleXQqyPEJba5YvG5ylyVqE-4CQg/view

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