

Received: 2015.01.19
Accepted: 2015.02.11
Published: 2015.07.03

RECK Gene Polymorphism is Associated with Susceptibility and Prognosis of Wilms' Tumor in Chinese Children

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABE Yang Yu*
ABE Yuanjun Hu*
BC Kaisheng Li
CDF Zhihong Chen
CD Hongmei Zhang
BC Lei Zhang

Department of Pediatric Surgery, Jinan Children's Hospital, Jinan, Shandong, P.R. China

* These authors contributed equally to this work and should be considered co-first authors

Corresponding Author: Yang Yu, e-mail: yayujnsd@163.com

Source of support: Departmental sources

Background: Wilms' tumor (WT) is the most common malignant renal tumor in children. Previous studies suggested the reversion-inducing, cysteine-rich protein with Kazal motifs (RECK) down-regulation might have a role in numerous human cancers. The current study was done to investigate the associations of RECK single-nucleotide polymorphisms (SNPs) with the WT susceptibility in Chinese children.





Material/Methods: We analyzed 2 SNPs (rs10972727 and rs11788747) in a total of 97 WT children and 194 healthy matched controls (1:2 ratio) by real-time PCR and PCR-RFLP genotyping analysis.

Results: We found that the G allele of rs11788747 in the RECK gene was significantly associated with WT in Chinese children (OR=0.7, 95% CI: 0.45–0.99; $P=0.042$); as with another SNP rs10972727, however, no statistically significant difference was detected. Further analysis showed there was also a statistically significant difference in genotype frequencies between terminal tumor stage ($P=0.026$) and metastatic groups ($P=0.002$).

Conclusions: The present data indicate that there is a significant association between mutant G of rs11788747 in RECK and WT risk. G carriers with advanced tumor stage or with metastasis might have an increased risk of WT.

MeSH Keywords: Genes, Tumor Suppressor • Genes, Wilms Tumor • Nephrology • Polymorphism, Single Nucleotide

Full-text PDF: <http://www.medscimonit.com/abstract/index/idArt/893606>

 1984  3  —  41



Background

Wilms' tumor (WT), also known as nephroblastoma, is the most frequent renal tumor occurring in children aged 0 to 15 years, especially among those younger than 6 years [1,2]. WT accounts for roughly 6% of all childhood cancers [4]; 5% of whom had bilateral involvement, and 1% of whom had a family history [3]. Thanks to the prospective clinical trials performed by the International Society of Pediatric Oncology – Renal Tumor Study Group (SIOP-RTSG, Europe) and the Children's Oncology Group (COG, formerly NWTSG, North America) [5], most patients ($\geq 85\%$) affected by WT can be successfully cured. However, some studies released surveys reporting that there are still a few children who may have a poor prognosis or relapse with current therapies, 50% of whom will die despite intensive re-treatment [6,7].

It has been proven that genetic variants are strongly associated with the development of WT. Several gene *loci* involved in disease outbreak have been identified. Mutations in WT1 or epigenetic defects on chromosome 11p15 contribute to the major genetic susceptibility locus [8]. Previous studies have reported several non-WT1 *loci* with smaller effects on the genetic predisposition for WT, including p53 gene [9], insulin-like growth factor-II gene [10], CTNNB1 gene [11], and H19 [12]. However, less than half of WT cases are attributable to known genes that are associated with WT risk; therefore, the exact pathogenesis of most WT cases remains unknown and identification of novel genetic *loci* is urgently needed.

The reversion-inducing cysteine-rich protein with Kazal motifs (RECK) gene, known as a transformation suppressor gene, can restrain tumor invasion and metastasis through suppression of matrix metalloproteinases (MMPs), including MMP-4 and MMP-9 [13]. MMPs proteolytically degrade extracellular matrix proteins, which is critical for tumor metastasis and invasion [14]. Celiker et al. reported that the expression of MMP-4 has an influence on progression of WT [15]. RECK is expressed in a number of normal tissues, but it appears to be down-regulated in several types of cancers, including esophageal cancer [16], breast cancer [17], lung cancer [18], colorectal cancer [19], osteosarcoma [20], gastric carcinoma [21], prostatic cancer [22], oral cancer [23], pancreatic cancer [24], and cholangiocarcinoma [25]. Moreover, clinical investigations have demonstrated that high expression of RECK in tumor tissues usually contributes to increasing survival rates and reducing tumor invasion [26]. Moreover, Hawthorn et al. [27] analyzed WT using single-nucleotide polymorphism (SNP) mapping array-based comparative genomic hybridization and found chromosomal deletion in 9q (RECK gene locates on 9q13-p12). Therefore, there might be an association between RECK gene and risk of WT.

Although it is well documented that RECK has an impact on metastasis and prognosis of human cancers, RECK gene SNPs

in WT susceptibility and clinical features remains poorly characterized. To obtain adequate power for assessing the potential association, we chose SNPs with minor allele frequencies of $>5\%$ [28]. Furthermore, rs10972727 and rs11788747 SNPs both were previously identified to be potentially associated with several types of human cancers, including oral cancer [29], non-small cell lung cancer [30], and hepatocellular carcinoma [31]. Therefore, the purpose of our study was to determine whether the 2 SNPs (rs10972727 and rs11788747) in RECK gene were associated with susceptibility to WT in Chinese children.

Material and Methods

Study participants and ethical statement

This case-control study received approval from the Human Research Ethics Board of Jinan Children's Hospital. A total of 291 study participants – 97 WT children and 194 healthy controls based on an age-sex-matched pair with 1: 2 ratio – were identified at the Jinan Children's Hospital. All the participants were Han Chinese. Written informed consent was obtained from parents of each participant before inclusion in the study. There were 41 male and 56 female patients, and the mean age at the time of surgery was 3.3 years. All patients received standard management described by SIOP-RTSG. All clinicopathological features of WT patients were retrieved from their medical records.

The patients' histopathological types and cancer grading were determined according to classification of renal tumor of childhood defined by SIOP-RTSG [32]. Accordingly, 43 (44.3%) out of 97 cases were characterized as WT stage I, 35 (36.1%) as stage II, 12 (12.4%) as stage III, and 7 (7.2%) as stage IV. According to the prognostic group, histology was favorable in 75 cases and unfavorable in 22. Moreover, no case had bilateral WT. According to the histologic type, there were 26 cases with blastemal type WT, 8 with diffuse anaplasia, 9 with focal anaplasia, 17 with epithelial, and 37 with mixed.

Genotyping of RECK

Genomic DNA was extracted by QIAamp DNA blood mini kits (Qiagen, Valencia, CA) according to the instructions of the manufacturer. RECK genotype polymorphisms (rs10972727 and rs11788747) were determined by polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP) method. PCR was carried out in a reaction mixture of 10 μ L containing 5–8 μ L DNA template, 0.5 U of Taq biocatalysts, 1.8 mmol/L Mg²⁺, 2.4 μ L dNTPs (Promega, Madison, WI), and 200 nM of each primer. The 2 SNPs were genotyped according to the methods described by Chung et al. [31]. Primers

Table 1. The distributions of demographical characteristics in 194 healthy controls and 97 patients with WT.

Variable	Patients (n=97)	Controls (n=194)	P-value
Age (years)	3.3±1.72	3.4±1.69	0.874
Gender (M/F)	41/56	83/111	0.177
Tumor stage			
I+II	78		
III+IV	19		
Histologic type			
Blastemal	26		
Diffuse anaplasia	8		
Focal anaplasia	9		
Epithelial	17		
Mixed	37		
Prognostic group			
Favorable histology	75		
Unfavorable histology	22		
Tumor size			
>500 g	12		
≤500 g	85		
Metastasis (yes,%)	16		
Relapse (yes,%)	6		
Family history (yes,%)	5		

WT – Wilms' tumor; M – male; F – female.

for rs10972727 were 5'-GTAGAAGAAGTGACTGATCC-3' and 5'-ATCTGACTCCGAAGATAACC-3'. The primers for the rs11788747 were 5'-TTCTATCAGGTCATGGAACA-3' and 5'-TGCGGTTAAGACTGGAGAAG-3'. The PCR cycling conditions were: initial denaturation at 94°C for 5 min, followed by 35 cycles of 1 min at 94°C, at 60°C for 30 s, and at 72°C for 1min, with a final extension at 72°C for 10 min. To verify results from PCR-CTPP, approximately 10% of the sample analysis was a duplication and each genotype was determined by the DNA sequence analysis.

Statistical analysis

Statistical analysis was done by using SPSS, version 19.0. For each polymorphism, Hardy-Weinberg equilibrium was analyzed to compare the observed and expected genotype frequencies using the standard χ^2 test or Fisher's exact test. The differences in distributions of genotypes and alleles between cases and controls were assessed by χ^2 tests. The estimated genotype-specific risks are presented as odds ratios (ORs). In all cases, the wild-type genotype was used as a reference group. The difference was considered significant if a P-value was <0.05.

Results

Demographics of WT patients and healthy controls are listed in the Table 1. There was no difference between cases and controls in age or sex. Five out of 97 cases had a family history of WT, 6 cases had relapse, and 16 had metastasis. In the present study, distributions of genotypes in cases and controls were in agreement with Hardy-Weinberg equilibrium (rs10972727, P=0.349 and P=0.121; and rs11788747, P=0.519 and P=0.123, respectively).

Association of the 2 SNPs with the risk of WT

Table 2 shows the genotype and allele frequencies of the 2 SNPs (rs10972727 and rs11788747) in RECK gene. No significant difference between cases and controls was observed for distribution of rs10972727 genotype, rs11788747 genotype, and rs11788747 allele. However, we found that the allele G of rs11788747 SNP was significantly associated with an increased risk of WT (OR=0.7, 95%CI: 0.45-0.99; P=0.042). Moreover, although when taking the AA genotype as a reference, we found

Table 2. Distribution of the RECK genotypes and alleles in Chinese children with WT and healthy controls.

	WT (n=97)		Controls (n=194)		OR (95% CI)	P-value
rs10972727						
Genotype						
TT	54	(55.7%)	109	(56.4%)	Reference	
TA	39	(38.1%)	78	(40.0%)	1.0	(0.60–1.64) 0.971
AA	4	(6.2%)	7	(3.7%)	0.9	(0.24–3.09) 0.826
TA+AA	43		85		1.0	(0.60–1.60) 0.933
Allele					1.0	(0.65–1.45) 0.819
T	147		296			
A	47		92			
rs11788747						
Genotype						
AA	49	(50.5%)	120	(61.8%)	Reference	–
AG	38	(39.2%)	62	(32.0%)	0.7	(0.39–1.12) 0.127
GG	10	(10.3%)	12	(6.2%)	0.5	(0.20–1.21) 0.116
AG+GG	48		74		0.6	(0.38–1.03) 0.065
Allele					0.7	(0.45–0.99) 0.042*
A	136		302			
G	58		86			

* P-value <0.05.

that AG + GG genotype was not statistically significantly associated with the risk of WT, there was a pronounced trend that carriers of 1 variant combined genotype had an increasing risk of WT (OR=0.6, 95%CI: 0.38–1.03; P=0.065).

Stratification analysis

Further analysis was conducted to investigate the associations between distribution of the genotype and allele of rs11788747 polymorphisms and clinicopathological features of WT patients. As shown in Table 3, although there was no significant difference in distribution of the genotype, allele G carriers with advanced tumor stage (P=0.026) had an increased risk of WT, as did those who had metastasis (P=0.002).

Discussion

The findings of this novel study provide evidence of the effects of SNPs of RECK on WT susceptibility and clinicopathologic status association. Allele G of rs10972727 SNP significantly increased WT risk. Various lines of evidence have found that tumor stage and metastasis are the risk factors for development of WT.

In the current study, we explored the association of RECK gene and WT risk, and subsequently analyzed the effects of combinations of functionally related polymorphisms and clinicopathological features of WT patients. To the best of our knowledge, this is the first study examining the association of RECK gene polymorphism with WT risk, although several previous studies have reported on its association with several other types of human cancers. As the most frequent renal tumor occurring in children, although WT has a high survival rate, 25% of WT children may have a poor prognosis or relapse with current therapies, 50% of whom will die despite intensive re-treatment. Moreover, little is known about the exact pathogenesis of most WT. Therefore, it is urgent for us to identify novel genetic loci that might be associated with WT risk.

It has been proven that the IGF pathway plays a role in development of WT. The IGF pathway is a complex signaling system stimulated by insulin-like growth factors (IGFs), which can be produced by almost any tissue in the body and has an important effect on growth, development, and survival in many different cell types [33]. The expression of IGF2 was found to be increased in WT. Overexpression of IGF2, activating the insulin signaling pathway, results in disorder of protein synthesis, cell cycle and cell growth, and blocks apoptosis [34]. Furthermore,

Table 3. Frequencies of genotype and allele of rs11788747 in RECK gene and the clinicopathological features in WT patients.

Variable	AA	AG+GG	P-value	A	G	P-value
Age (>5/≤5 years)	35/14	40/8	0.162	103/33	47/11	0.420
Gender (M/F)	19/30	22/26	0.482	56/80	26/32	0.637
Tumor stage			0.760			0.026*
I+II	40	38		115	41	
III+IV	9	10		21	17	
Prognostic group			0.589			0.053
Favorable histology	39	36		129	41	
Unfavorable histology	10	12		27	17	
Tumor size			0.203			0.068
>500 g	4	8		13	11	
≤500 g	45	40		123	47	
Metastasis (Y/N)	5/44	11/37	0.092	15/121	17/41	0.002*
Relapse (Y/N)	2/47	4/44	0.385	6/130	6/52	0.116
Family history (Y/N)	2/47	3/45	0.629	5/131	5/53	0.154

M – male; F – female; Y – yes; N – no. * *P*-value <0.05.

Yamamoto et al. [35] indicated that reduced RECK could increase IGF2 expression. The interaction between RECK gene and IGF gene might have a potential influence on susceptibility to WT. A study by Huang et al. [36] demonstrated down-regulation of RECK gene expression in patients with WT. Therefore, we conducted this study to determine whether RECK gene is associated with WT risk.

In the current study, our findings suggest that mutant of rs10972727 in RECK had an impact on increasing WT risk. In addition, allele G carriers with advanced tumor stage involving metastasis had an increasing risk of WT. Advanced tumor stage and metastasis are responsible for patient mortality in most tumors [37–39]. Masui et al. [24] found the level of RECK expression determined the prognosis of pancreatic cancer and tumors, with overexpression of RECK significantly decreasing invasiveness compared with RECK-negative tumors, revealing the potential value of RECK as a prognostic molecular marker for pancreatic cancer. Zhang et al. [40] reported that silenced RECK gene was associated with poor survival in hepatocellular carcinoma. Chung et al. [31] showed that those who carried rs10814325 with at least 1 C allele had a higher risk of hepatocellular carcinoma. Zhou et al. [41], after a follow-up of salivary adenoid cystic carcinoma patients, revealed that expression of RECK and MMP-2 gene were correlated with tumor progression. In our study, we found a correlation between rs10972727 in RECK and tumor stage and metastasis. These results suggest that RECK gene may predict the prognosis of WT. However, the exact physiological mechanism by which RECK

influences progression of WT remains unclear. Further research is urgently needed to explore the interaction of RECK and WT.

Several limitations of our study should be noted when interpreting the results. Firstly, the primary weakness of this study is that the small sample size may affect the power in statistical analysis. Secondly, the results were not replicated in additional individuals, and this might contribute to potential false-positive errors. Moreover, the method used to select potentially functional SNPs as targets by using a web-based tool might have led to some positive or negative errors. Finally, we did not perform a functional study to further reveal the mechanism by which the genetic polymorphisms in RECK affect WT risk.

Conclusions

Data from the present data indicate that rs10972727 in RECK gene is not associated with WT risk in Chinese children, but the association between mutant G of rs11788747 in RECK and WT risk was shown. G carriers with advanced tumor stage or with metastasis might have an increased risk of WT. Therefore, further research is necessary to reveal the mechanism by which the genetic polymorphisms in RECK affect the WT risk.

Conflict of interest

The authors declare that they have no conflict of interest.

References:

1. Breslow N, Olshan A, Beckwith JB, Green DM: Epidemiology of Wilms tumor. *Med Pediatr Oncol*, 1993; 21: 172–81
2. Junien C, Henry I: Genetics of Wilms' tumor: a blend of aberrant development and genomic imprinting. *Kidney Int*, 1994; 46: 1264–79
3. Radojevic-Skodric S, Basta-Jovanovic G, Brasanac D et al: Survivin gene promoter -31 G/C polymorphism is associated with Wilms tumor susceptibility in Serbian children. *J Pediatr Hematol Oncol*, 2012; 34: e310–14
4. Kalapurakal JA, Nan B, Norkool P et al: Treatment outcomes in adults with favorable histologic type Wilms tumor-an update from the National Wilms Tumor Study Group. *Int J Radiat Oncol Biol Phys*, 2004; 60: 1379–84
5. Pritchard-Jones K, Pieters R, Reaman GH et al: Sustaining innovation and improvement in the treatment of childhood cancer: lessons from high-income countries. *Lancet Oncol*, 2013; 14: e95–e103
6. Dome JS, Liu T, Krasin M et al: Improved survival for patients with recurrent Wilms tumor: the experience at St. Jude Children's Research Hospital. *J Pediatr Hematol Oncol*, 2002; 24: 192–98
7. Malogolowkin M, Cotton CA, Green DM et al: Treatment of Wilms tumor relapsing after initial treatment with vincristine, actinomycin D, and doxorubicin. A report from the National Wilms Tumor Study Group. *Pediatr Blood Cancer*, 2008; 50: 236–41
8. Scott RH, Stillier CA, Walker L, Rahman N: Syndromes and constitutional chromosomal abnormalities associated with Wilms tumour. *J Med Genet*, 2006; 43: 705–15
9. Defavery R, Lemos JA, Kashima S et al: Analysis of the p53 gene by PCR-SSCP in ten cases of Wilms' tumor. *Sao Paulo Med J*, 2000; 118: 49–52
10. Wang WH, Duan JX, Vu TH, Hoffman AR: Increased expression of the insulin-like growth factor-II gene in Wilms' tumor is not dependent on loss of genomic imprinting or loss of heterozygosity. *J Biol Chem*, 1996; 271: 27863–70
11. Koesters R, Ridder R, Kopp-Schneider A et al: Mutational activation of the beta-catenin proto-oncogene is a common event in the development of Wilms' tumors. *Cancer Res*, 1999; 59: 3880–82
12. Maschietto M, Charlton J, Perotti D et al: The IGF signalling pathway in Wilms tumours – a report from the ENCCA Renal Tumours Biology-driven drug development workshop. *Oncotarget*, 2014; 5: 8014–26
13. Clark JC, Thomas DM, Choong PF, Dass CR: RECK – a newly discovered inhibitor of metastasis with prognostic significance in multiple forms of cancer. *Cancer Metastasis Rev*, 2007; 26: 675–83
14. Xie J, Tan ZH, Tang X et al: MiR-374b-5p suppresses RECK expression and promotes gastric cancer cell invasion and metastasis. *World J Gastroenterol*, 2014; 20: 17439–47
15. Celiker MY, Wang M, Atsidaftos E et al: Inhibition of Wilms' tumor growth by intramuscular administration of tissue inhibitor of metalloproteinases-4 plasmid DNA. *Oncogene*, 2001; 20: 4337–43
16. Qi M, Li JS, Li Y: [Clinicopathological significance of expressions of RECK and MMP-2 in esophageal squamous carcinoma]. *Zhonghua Zhong Liu Za Zhi*, 2010; 32: 283–85 [in Chinese]
17. Span PN, Sweep CG, Manders P et al: Matrix metalloproteinase inhibitor reversion-inducing cysteine-rich protein with Kazal motifs: a prognostic marker for good clinical outcome in human breast carcinoma. *Cancer*, 2003; 97: 2710–15
18. Takenaka K, Ishikawa S, Kawano Y et al: Expression of a novel matrix metalloproteinase regulator, RECK, and its clinical significance in resected non-small cell lung cancer. *Eur J Cancer*, 2004; 40: 1617–23
19. Takeuchi T, Hisanaga M, Nagao M et al: The membrane-anchored matrix metalloproteinase (MMP) regulator RECK in combination with MMP-9 serves as an informative prognostic indicator for colorectal cancer. *Clin Cancer Res*, 2004; 10: 5572–79
20. Xu J, Wu S, Shi X: Expression of matrix metalloproteinase regulator, RECK, and its clinical significance in osteosarcoma. *J Orthop Res*, 2010; 28: 1621–25
21. Song SY, Son HJ, Nam E et al: Expression of reversion-inducing-cysteine-rich protein with Kazal motifs (RECK) as a prognostic indicator in gastric cancer. *Eur J Cancer*, 2006; 42: 101–8
22. Rabien A, Burkhardt M, Jung M et al: Decreased RECK expression indicating proteolytic imbalance in prostate cancer is associated with higher tumor aggressiveness and risk of prostate-specific antigen relapse after radical prostatectomy. *Eur Urol*, 2007; 51: 1259–66
23. Long NK, Kato K, Yamashita T et al: Hypermethylation of the RECK gene predicts poor prognosis in oral squamous cell carcinomas. *Oral Oncol*, 2008; 44: 1052–58
24. Masui T, Doi R, Koshiba T et al: RECK expression in pancreatic cancer: its correlation with lower invasiveness and better prognosis. *Clin Cancer Res*, 2003; 9: 1779–84
25. Li Y, Zhang Y, Zheng Q: Expression of RECK gene and MMP-9 in hilar cholangiocarcinoma and its clinical significance. *J Huazhong Univ Sci Technol Med Sci*, 2005; 25: 552–54
26. Kang HG, Kim HS, Kim KJ et al: RECK expression in osteosarcoma: correlation with matrix metalloproteinases activation and tumor invasiveness. *J Orthop Res*, 2006; 25: 696–702
27. Hawthorn L, Cowell JK: Analysis of wilms tumors using SNP mapping array-based comparative genomic hybridization. *PLoS One*, 2011; 6: e18941
28. Eisenberg I, Hochner H, Sadeh M et al: Establishment of the genomic structure and identification of thirteen single-nucleotide polymorphisms in the human RECK gene. *Cytogenet Genome Res*, 2002; 97: 58–61
29. Chung TT, Pan MS, Kuo CL et al: Impact of RECK gene polymorphisms and environmental factors on oral cancer susceptibility and clinicopathologic characteristics in Taiwan. *Carcinogenesis*, 2011; 32: 1063–68
30. Chen X, Jiang F, Shi N et al: RECK gene polymorphisms influence NSCLC susceptibility, but not the chemotherapy response status in Chinese cohort. *Cell Biochem Biophys*, 2014; 69: 567–71
31. Chung TT, Yeh CB, Li YC et al: Effect of RECK gene polymorphisms on hepatocellular carcinoma susceptibility and clinicopathologic features. *PLoS One*, 2012; 7: e33517
32. Vujanic GM, Sandstedt B, Harms D et al: Revised International Society of Paediatric Oncology (SIOP) working classification of renal tumors of childhood. *Med Pediatr Oncol*, 2002; 38: 79–82
33. Scott J, Cowell J, Robertson ME et al: Insulin-like growth factor-II gene expression in Wilms' tumour and embryonic tissues. *Nature*, 1985; 317: 260–62
34. Gallagher EJ, LeRoith D: The proliferating role of insulin and insulin-like growth factors in cancer. *Trends Endocrinol Metab*, 2010; 21: 610–18
35. Yamamoto M, Matsuzaki T, Takahashi R et al: The transformation suppressor gene Reck is required for postaxial patterning in mouse forelimbs. *Biol Open*, 2012; 1: 458–66
36. Huang CC, Gadd S, Breslow N et al: Predicting relapse in favorable histology Wilms tumor using gene expression analysis: a report from the Renal Tumor Committee of the Children's Oncology Group. *Clin Cancer Res*, 2009; 15: 1770–78
37. Lee JH, Welch DR: Suppression of metastasis in human breast carcinoma MDA-MB-435 cells after transfection with the metastasis suppressor gene, KISS-1. *Cancer Res*, 1997; 57: 2384–87
38. Welch DR, Steeg PS, Rinker-Schaeffer CW: Molecular biology of breast cancer metastasis. Genetic regulation of human breast carcinoma metastasis. *Breast Cancer Res*, 2000; 2: 408–16
39. Yang J, Mani SA, Donaher JL et al: Twist, a master regulator of morphogenesis, plays an essential role in tumor metastasis. *Cell*, 2004; 117: 927–39
40. Zhang C, Ling Y, Zhang C et al: The silencing of RECK gene is associated with promoter hypermethylation and poor survival in hepatocellular carcinoma. *Int J Biol Sci*, 2012; 8: 451–58
41. Zhou X, Huang S, Jiang L et al: Expression of RECK and MMP-2 in salivary adenoid cystic carcinoma: Correlation with tumor progression and patient prognosis. *Oncol Lett*, 2014; 7: 1549–55