

## Original Article

# Interleukin-16 rs4778889 polymorphism contributes to the development of renal cell cancer in a Chinese population

Zongping Wang, Yipeng Xu, Shaoxing Zhu

Department of Urology, Zhejiang Cancer Hospital, Hangzhou 310022, Zhejiang, China

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**Abstract:** We conducted a case-control study to assess the role of IL-16 rs4778889, rs11556218 and rs8034928 polymorphisms in the development of RCC. This case-control study included 181 patients with RCC and 278 control patients. The genotyping of IL-16 rs4778889, rs11556218 and rs8034928 polymorphisms were performed using polymerase chain reaction (PCR) combined with restriction fragment length polymorphism analysis. By  $\chi^2$  test, we found that patients with RCC were more likely to suffer from hypertension ( $\chi^2 = 9.06$ ,  $P = 0.003$ ) and diabetes ( $\chi^2 = 7.91$ ,  $P = 0.005$ ). By unconditional logistic regression analysis, the CC genotype of rs4778889 was associated with an increased risk of RCC compared to TT genotype, and the adjusted OR (95% CI) was 3.58 (1.59-8.31). In dominant model and recessive model, we found the rs4778889 polymorphisms were associated with an elevated increased risk of RCC, and the adjusted ORs (95% CI) were 1.64 (1.10-2.43) and 3.07 (1.40-6.98), respectively. We found that rs4778889 polymorphism had interaction with hypertension (OR = 2.44, 95% CI = 1.01-6.00) and diabetes (OR = 6.91, 95% CI = 1.44-37.05) in the risk of RCC. In conclusion, the results of our study suggested an association between the IL-16 rs4778889 polymorphism and an elevated risk of RCC.

**Keywords:** Interleukin-16, polymorphism, renal cell cancer

## Introduction

Renal cell cancer (RCC) is a complex-trait disease, and is the ninth most common tumor in men and the fourteenth most common tumor in women [1]. The incidence of RCC is increasing steadily, and it increased by 2% and 3% per year in developed countries [1]. In the Chinese population, there were 44,375 new cases with RCC per 10,000 people [2]. The process of RCC is involved in many complex factors, such as hypertension, cigarette smoking, alcohol drinking, occupational exposures to chemicals and family history of RCC [3-6]. However, not all patients who exposed to the risk factors of RCC would develop RCC, which suggests that genetic factors may contribute to the development of this cancer.

An increasing amount of evidence has reported that the inflammation contributes to the pathogenesis of RCC [7-10], and that several cytokines are associated with the arterial wall

inflammatory process. Variations in genes related to the inflammatory system may alter the pattern of proinflammatory cytokine production, and thus the development of RCC, affecting predisposition and prevalence [9, 10].

Interleukin-16 (IL-16) is a cytokine with many important functions, and is involved in several contradictory processes. It plays key roles in activating CD4+ T cells, macrophages, monocytes, eosinophils, and dendritic cells [11]. IL-16 is reported to be involved in promoting the secretion of tumor-associated inflammatory cytokines which contribute to the process of tumorigenesis, such as tumor necrosis factor- $\alpha$ , IL-1 $\beta$ , IL-6 and IL-15 [12-14]. Only one previous study reported the association between IL-16 gene polymorphisms and development and RCC (Zhu et al., 2010). Three functional polymorphisms in the IL-16 gene rs4778889, rs11556218 and rs8034928 are found to be correlated with inflammatory diseases [15, 16]. We conducted a case-control study to assess

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**Table 1.** Demographic and clinical characteristics of patients with RCC and control subjects

Characteristics	Cases	%	Controls	%	t or $\chi^2$ test	P value
Age, years	54.65±9.34		53.76±9.10		1.01	0.16
Sex						
Male	119	65.75	188	67.63		
Female	62	34.25	90	32.37	0.17	0.68
Cigarette smoking						
Never	102	56.35	180	64.75		
Ever	79	43.65	98	35.25	3.26	0.07
Alcohol drinking						
Never	96	53.04	154	55.40		
Ever	85	46.96	124	44.60	0.24	0.62
Hypertension						
No	129	71.27	231	83.09		
Yes	52	28.73	47	16.91	9.06	0.003
Diabetes						
No	156	86.19	261	93.88		
Yes	25	13.81	17	6.12	7.81	0.005
Family history of cancer						
Never	169	93.37	265	95.32		
Ever	12	6.63	13	4.68	0.81	0.37
Stage						
I-II	113	62.43				
III-IV	68	37.57				
Histology						
Clear cell	147	81.22				
Papillary	8	4.42				
Chromophobe	17	9.39				
Others	9	4.97				

the role of IL-16 rs4778889, rs11556218 and rs8034928 polymorphisms in the development of RCC.

### Material and methods

#### Subjects

This case-control study included 181 patients with RCC and 278 control patients. All the RCC patients were enrolled in our hospital between February 2013 and December 2014, and patients with RCC were newly diagnosed and confirmed by pathological tissue. Patients who had primary tumors other than RCC, tumors of an unknown origin or any histopathological diagnosis other than RCC were excluded.

Cancer free control subjects were randomly enrolled from individuals seeking for health

check-up in our hospital during the same period time.

The demographic and clinical characteristics of patients with RCC were collected from a self-designed questionnaire. The demographic data included age, gender, cigarette smoking, cigarette smoking, alcohol drinking, hypertension, diabetes and family history of cancer. The clinical data included TNM stage and histology. The TNM stage was determined by pathologists based on the American Joint Committee on Cancer TNM classification.

Written informed consents were obtained from patients with RCC and control subjects prior to enrolling into our study. This work was approved by the Institute Research Ethics Committee of our hospital.

#### Genotyping

Five mL peripheral venous blood sample was collected from each patient with RCC and control subject after enrollment into this study. The blood samples were stored at -20°C until use.

Genomic DNA was isolated from peripheral blood lymphocytes using Qiagen blood mini kit (Qiagen, Germany) based on the manufacturer's protocol. The genotyping of IL-16 rs4778889, rs11556218 and rs8034928 polymorphisms were performed using polymerase chain reaction (PCR) combined with restriction fragment length polymorphism analysis. The forward and reverse primers used to amplify IL-16 rs4778889 were 5'-CAATGC-CAGTCCCTCCACA-3' and 5'-AGGTCATGGGCT-CATACTG-3', respectively; the forward and reverse primers for IL-16 rs11556218 were 5'-CTGGTCCTGACTTCCTTTGG-3' and 5'-TGG-TGCGTGGTCCCCTTG-3', respectively; the forward and reverse primers for IL-16 rs8034928 were 5'-CCTTATTTGAAGAGAGC-3' and 5'-TGC-AGATTCCAGGTTTC-3', respectively. For PCR amplification, amplification was performed as follows: 95°C for 5 min, 30 cycles of 95°C for

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**Table 2.** Genotype frequencies of IL-16 rs4778889, rs11556218 and rs8034928 among the cases with RCC and controls and their association with risk of RCC

Genotypes	Patients	%	Controls	%	$\chi^2$ test	P value	HWE	OR (95% CI) <sup>1</sup>	P value
<b>rs4778889</b>									
Codominant									
TT	82	45.30	160	57.55				1.0 (Ref.)	-
TC	77	42.54	106	38.13				1.42 (0.93-2.15)	0.08
CC	22	12.15	12	4.32	12.75	0.002	0.28	3.58 (1.59-8.31)	<0.001
Dominant									
TT	82	45.30	160	57.50				1.0 (Ref.)	-
TC+CC	99	54.70	118	42.45	6.6	0.01		1.64 (1.10-2.43)	0.01
Recessive									
TT+TC	159	87.85	266	95.68				1.0 (Ref.)	-
CC	22	12.15	12	4.32	9.82	0.002		3.07 (1.40-6.98)	0.002
<b>rs11556218</b>									
Codominant									
TT	94	51.93	155	55.76				1.0 (Ref.)	-
TG	75	41.44	108	38.85				1.15 (0.76-1.72)	0.5
GG	12	6.63	15	5.40	0.76	0.68	0.49	1.32 (0.54-3.16)	0.5
Dominant									
TT	94	51.60	155	55.70				1.0 (Ref.)	-
TG+GG	87	48.07	123	44.24	0.65	0.42		1.17 (0.79-1.73)	0.42
Recessive									
TT+TG	169	93.37	263	94.60				1.0 (Ref.)	-
GG	12	6.63	15	5.40	0.3	0.58		1.24 (0.52-2.93)	0.58
<b>rs8034928</b>									
Codominant									
TT	95	52.49	154	55.40				1.0 (Ref.)	-
TC	73	40.33	109	39.21				1.09 (0.72-1.64)	0.68
CC	13	7.18	15	5.40	0.78	0.68	0.45	1.40 (0.59-3.32)	0.39
Dominant									
TT	95	52.49	154	55.40				1.0 (Ref.)	-
TC+CC	86	47.51	124	44.60	0.37	0.54		1.12 (0.76-1.67)	0.54
Recessive									
TT+TC	168	92.82	263	94.60				1.0 (Ref.)	-
CC	13	7.18	15	5.40	0.61	0.43		1.36 (0.58-3.14)	0.43

<sup>1</sup>Adjusted for sex, age, hypertension and diabetes.

30s, 63°C for 30 s, and 72°C for 30 s and a final extension step of 72°C for 10 min. The product sizes for IL-16 rs4778889, rs11556218 and rs8034928 were 90 bp, 136 bp and 171 bp, respectively.

### Statistical analysis

The demographic and clinical data of patients with RCC and control subjects were shown as mean  $\pm$  standard deviation and frequency (percentage) of study subjects. The demographic and clinical data between patients with RCC

and control subjects were compared by t-test or  $\chi^2$ -test. Hardy-Weinberg equilibrium of genetic distributions in controls was tested with a goodness of fit  $\chi^2$  test with one degree of freedom, which was used to compare the observed genotype frequencies in the subjects with the expected genotype frequencies. Unconditional logistic regression was used to assess the IL-16 rs4778889, rs11556218 and rs8034928 polymorphisms and the risk of RCC, and the results were expressed by odds ratios (OR) and its 95% confidence intervals (95% CI). A P-value less than 0.05 were considered statistically sig-

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**Table 3.** Stratification analysis between *IL16* rs4778889 and risk of RCC by cigarette smoking, alcohol drinking, hypertension and diabetes

Variables	Patients		Controls		OR (95% CI)	P value
	TT	TC+CC	TT	TC+CC		
Cigarette smoking	82	99	160	118		
Never	48	54	104	76	1.54 (0.92-2.58)	0.08
Ever	34	45	56	42	1.76 (0.93-3.36)	0.06
Alcohol drinking						
Never	44	52	88	66	1.58 (0.91-2.72)	0.08
Ever	38	47	72	52	1.71 (0.95-3.11)	0.06
Hypertension						
No	59	70	129	102	1.50 (0.95-2.37)	0.07
Yes	23	29	31	16	2.44 (1.01-6.00)	0.03
Diabetes						
No	74	82	147	114	1.43 (0.94-2.17)	0.08
Yes	8	17	13	4	6.91 (1.44-37.05)	0.005

nificant. Statistical analysis was done using statistical package SPSS 16.0 software (SPSS, Chicago, IL, USA).

### Results

The baseline characteristics of patients with RCC and control subjects were described in **Table 1**. By  $\chi^2$  test, we found that patients with RCC were more likely to suffer from hypertension ( $\chi^2 = 9.06$ ,  $P = 0.003$ ) and diabetes ( $\chi^2 = 7.91$ ,  $P = 0.005$ ). However, no significant difference was found between patients with RCC and control subjects in terms of age ( $t = 7.91$ ,  $P = 0.16$ ), sex ( $\chi^2 = 0.17$ ,  $P = 0.68$ ), cigarette smoking ( $\chi^2 = 3.26$ ,  $P = 0.07$ ), alcohol drinking ( $\chi^2 = 0.24$ ,  $P = 0.62$ ) and family history of cancer ( $\chi^2 = 0.81$ ,  $P = 0.37$ ). Of 181 patients with RCC, 113 (62.43%) at I-II TNM stage, 68 (37.57%) at III-IV TNM stage, and 147 (81.22%) were clear cell RCC.

By  $\chi^2$  test with one degree of freedom, we found the genotype frequencies of *IL-16* rs4778889, rs11556218 and rs8034928 did not deviate from HWE, and the  $P$  values (for HWE) were 0.34, 0.22 and 0.45, respectively (**Table 2**). We found significant differences in the genotype frequencies of rs4778889 ( $\chi^2 = 12.75$ ,  $P = 0.002$ ); however, rs11556218 and rs8034928 exhibited no such differences. By unconditional logistic regression analysis, we found that the CC genotype of rs4778889 was associated

with an increased risk of RCC compared to TT genotype, and the adjusted OR (95% CI) was 3.58 (1.59-8.31). In dominant model and recessive model, we found the rs4778889 polymorphisms were associated with an elevated increased risk of RCC, and the adjusted ORs (95% CI) were 1.64 (1.10-2.43) and 3.07 (1.40-6.98), respectively.

Moreover, we conducted stratification analysis between rs4778889 and risk of RCC by cigarette smoking, alcohol drinking, hypertension and diabetes (**Table 3**). We found that rs4778889 polymorphism

was associated with development of RCC regardless of cigarette smoking and alcohol drinking, but this SNP had interaction with hypertension (OR = 2.44, 95% CI = 1.01-6.00) and diabetes (OR = 6.91, 95% CI = 1.44-37.05) in the risk of RCC.

### Discussion

In the present study, we investigated whether the three functional SNPs in *IL-16* rs4778889, rs11556218 and rs8034928 could influence the susceptibility to RCC in a Chinese population. We found that the CC genotype of rs4778889 was associated with an increased risk of RCC compared to TT genotype, and we revealed the *IL-16* rs4778889 polymorphisms were associated with an elevated increased risk of RCC in dominant model and recessive models, especially in patients with hypertension or diabetes. Therefore, our results suggest that *IL-16* rs4778889 polymorphism may play an important role in the development of RCC, and this gene could be used as a genetic marker for identification the development of RCC in a Chinese population.

*IL-16* is a multifunctional cytokine and plays a critical role in inflammatory diseases and tumor growth as well as tumor procession. Previous studies have reported that *IL-16* gene polymorphisms are association with the development of various cancers, such as colorectal cancer,

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gastric cancer, nasopharyngeal carcinoma, hepatocellular carcinoma and glioma [17-21]. Gao et al. conducted a case-control study with 376 colorectal cancer patients and 220 gastric cancer patients in a Chinese population, and they found that the rs11556218 polymorphism was significantly associated with the susceptibility to colorectal cancer and gastric cancer patients [17]. In human nasopharyngeal carcinoma, Gao et al. conducted another study in a Chinese population with 206 nasopharyngeal cancer patients, and they reported that rs11556218 polymorphism contributes to the susceptibility to nasopharyngeal cancer [18]. Li et al. analyzed the association between three SNPs of IL-16 polymorphisms and development of HBV-related hepatocellular carcinoma, and they found that rs11556218 and rs4072111 were associated with susceptibility to chronic HBV infection and risk of hepatocellular carcinoma [19]. Azimzadeh et al. reported that IL-16 rs11556218 and rs4778889 polymorphisms could influence the development of colorectal cancer [20]. Qin et al. reported that IL-16 rs11556218 polymorphism was correlated with an elevated risk of nasopharyngeal carcinoma [21]. A recent meta-analysis reported that the IL-16 rs11556218 polymorphism was significantly correlated with elevated cancer risk in Asian population [22]. The above-mentioned studies suggest that IL-16 gene polymorphisms are associated with development of cancers.

Our study found that IL-16 rs4778889 polymorphism played a major role in susceptibility to RCC. A possible mechanism for IL-16 rs4778889 polymorphism in modulating the development of RCC is that the IL-16 rs4778889 polymorphism regulates the expression of serum levels of IL-16, and the over-expressed IL-16 is associated with the development of tumorigenesis of RCC. Only one previous study has reported that IL-16 -295 T>C polymorphism is significantly associated with development of RCC [23]. However, no studies reported the association between IL-16 rs4778889, rs11556218 and rs8034928 and development of RCC. Moreover, our study found that the rs4778889 polymorphism had interaction with hypertension and diabetes in the risk of RCC. Previous studies have reported that IL-16 expression was associated with development of type 2 diabetes mellitus and hypertension related diseases [24, 25]. Further studies with

large sample sizes are greatly required to confirm our study.

Two limitations in our study should be taken into consideration. First, patients with RCC and control subjects were selected from only one hospital, which would cause selection bias in our study. However, the genotype distributions of IL-16 rs4778889, rs11556218 and rs8034928 conform with the Hardy-Weinberg equilibrium in controls, which suggests that our population may represent the general population. Second, the sample size of our study is relatively small, which could reduce the statistical power to find differences between groups. Therefore, further studies with participants from multiple locations and a larger sample size are required to confirm our results.

In conclusion, the results of our study suggested an association between the IL-16 polymorphisms and an elevated risk of RCC, especially in patients with diabetes mellitus and hypertension. Our study offers insights into the influence of IL-16 on development of RCC.

### Disclosure of conflict of interest

None.

**Address correspondence to:** Dr. Zongping Wang, Department of Urology, Zhejiang Cancer Hospital, 38 Guangji Road, Hangzhou 310022, Zhejiang, China. Tel: +86-571-88128021; Fax: +86-571-88122523; E-mail: zongpzwang@sina.com

### References

- [1] International Agency for Research on Cancer (IARC). GLOBOCAN 2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012. [http://globocan.iarc.fr/Pages/fact\\_sheets\\_cancer.aspx](http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx). Accessed August 1, 2015.
- [2] Liu XL, Du JZ, Zhou YM, Shu QF, Li YG. Interleukin-16 polymorphism is associated with an increased risk of ischemic stroke. *Mediators Inflamm* 2013; 2013: 564750.
- [3] Facchini F, Chen YD, Reaven GM. Light-to-moderate alcohol intake is associated with enhanced insulin sensitivity. *Diabetes Care* 1994; 17: 115-9.
- [4] Vineis P, Alavanja M, Buffler P, Fontham E, Franceschi S, Gao YT, Gupta PC, Hackshaw A, Matos E, Samet J, Sitas F, Smith J, Stayner L, Straif K, Thun MJ, Wichmann HE, Wu AH, Zaridze D, Peto R, Doll R. Tobacco and cancer: re-

## IL-16 polymorphism and renal cell cancer

- cent epidemiological evidence. *J Natl Cancer Inst* 2004; 96: 99-106.
- [5] Adams KF, Leitzmann MF, Albanes D, Kipnis V, Moore SC, Schatzkin A, Chow WH. Body size and renal cell cancer incidence in a large US cohort study. *Am J Epidemiol* 2008; 168: 268-77.
- [6] Bellocco R, Pasquali E, Rota M, Bagnardi V, Tramacere I, Scotti L, Pelucchi C, Boffetta P, Corrao G, La Vecchia C. Alcohol drinking and risk of renal cell carcinoma: results of a meta-analysis. *Ann Oncol* 2012; 23: 2235-44.
- [7] Chang Y, Xu L, An H, Fu Q, Chen L, Lin Z, Xu J. Expression of IL-4 and IL-13 predicts recurrence and survival in localized clear-cell renal cell carcinoma. *Int J Clin Exp Pathol* 2015; 8: 1594-603.
- [8] Pan D, Xu L, Liu H, Zhang W, Zhu Y, Xu J, Gu J. Interleukin-11 receptor predicts post-operative clinical outcome in patients with early-stage clear-cell renal cell carcinoma. *Jpn J Clin Oncol* 2015; 45: 202-9.
- [9] Pu Y, Chen P, Zhou B, Zhang P, Wang Y, Song Y, Zhang L. Association between polymorphisms in IL27 gene and renal cell carcinoma. *Biomarkers* 2015; 20: 202-5.
- [10] Shibasaki N, Yamasaki T, Kanno T, Arakaki R, Sakamoto H, Utsunomiya N, Inoue T, Tsuruyama T, Nakamura E, Ogawa O, Kamba T. Role of IL13RA2 in Sunitinib Resistance in Clear Cell Renal Cell Carcinoma. *PLoS One* 2015; 10: e0130980.
- [11] Cruikshank WW, Center DM, Nisar N, Wu M, Natke B, Theodore AC, Kornfeld H. Molecular and functional analysis of a lymphocyte chemoattractant factor: association of biologic function with CD4 expression. *Proc Natl Acad Sci U S A* 1994; 91: 5109-13.
- [12] Kai H, Kitadai Y, Kodama M, Cho S, Kuroda T, Ito M, Tanaka S, Ohmoto Y, Chayama K. Involvement of proinflammatory cytokines IL-1beta and IL-6 in progression of human gastric carcinoma. *Anticancer Res* 2005; 25: 709-13.
- [13] Muc-Wierzgon M, Nowakowska-Zajdel E, Kokot T, Kozowicz A, Wiczowski A, Grochowska-Niedworok E, Mazurek U, Wierzgon J. Genetic dysregulation of TNF alpha and TNF alpha type II receptors in colon cancer at the II and III stage of disease. *J Biol Regul Homeost Agents* 2006; 20: 10-4.
- [14] Shanmugham LN, Petrarca C, Frydas S, Donelan J, Castellani ML, Boucher W, Madhappan B, Tete' S, Falasca K, Conti P, Vecchiet J. IL-15 an immunoregulatory and anti-cancer cytokine. *Recent advances. J Exp Clin Cancer Res* 2006; 25: 529-36.
- [15] Reich K, Westphal G, König IR, Mössner R, Krüger U, Ziegler A, Neumann C, Schnuch A. Association of allergic contact dermatitis with a promoter polymorphism in the IL16 gene. *J Allergy Clin Immunol* 2003; 112: 1191-4.
- [16] Hosseini-Farahabadi S, Tavakkol-Afshari J, Rafatpanah H, Farid Hosseini R, Khaje Daluei M. Association between the polymorphisms of IL-4 gene promoter (-590C>T), IL-13 coding region (R130Q) and IL-16 gene promoter (-295T>C) and allergic asthma. *Iran J Allergy Asthma Immunol* 2007; 6: 9-14.
- [17] Gao LB, Rao L, Wang YY, Liang WB, Li C, Xue H, Zhou B, Sun H, Li Y, Lv ML, Du XJ, Zhang L. The association of interleukin-16 polymorphisms with IL-16 serum levels and risk of colorectal and gastric cancer. *Carcinogenesis* 2009; 30: 295-9.
- [18] Gao LB, Liang WB, Xue H, Rao L, Pan XM, Lv ML, Bai P, Fang WL, Liu J, Liao M, Zhang L. Genetic polymorphism of interleukin-16 and risk of nasopharyngeal carcinoma. *Clin Chim Acta* 2009; 409: 132-5.
- [19] Li S, Deng Y, Chen ZP, Huang S, Liao XC, Lin LW, Li H, Peng T, Qin X, Zhao JM. Genetic polymorphism of interleukin-16 influences susceptibility to HBV-related hepatocellular carcinoma in a Chinese population. *Infect Genet Evol* 2011; 11: 2083-8.
- [20] Azimzadeh P, Romani S, Mohebbi SR, Kazemian S, Vahedi M, Almasi S, Fatemi SR, Zali MR. Interleukin-16 (IL-16) gene polymorphisms in Iranian patients with colorectal cancer. *J Gastrointest Liver Dis* 2011; 20: 371-6.
- [21] Qin X, Peng Q, Lao X, Chen Z, Lu Y, Lao X, Mo C, Sui J, Wu J, Zhai L, Yang S, Li S, Zhao J. The association of interleukin-16 gene polymorphisms with IL-16 serum levels and risk of nasopharyngeal carcinoma in a Chinese population. *Tumour Biol* 2014; 35: 1917-24.
- [22] Zhao Y, Tao L, Wang B, Nie P, Tang Y, Zhu M. Interleukin-16 gene polymorphisms rs4778-889, rs4072111, rs11556218, and cancer risk in Asian populations: a meta-analysis. *Genet Test Mol Biomarkers* 2014; 18: 174-82.
- [23] Zhu J, Qin C, Yan F, Wang M, Ding Q, Zhang Z, Yin C. IL-16 polymorphism and risk of renal cell carcinoma: association in a Chinese population. *Int J Urol* 2010; 17: 700-7.
- [24] Liu XL, Du JZ, Zhou YM, Shu QF, Li YG. Interleukin-16 polymorphism is associated with an increased risk of ischemic stroke. *Mediators Inflamm* 2013; 2013: 564750.
- [25] Zak KP, Kondratskaia IN, Mel'nichenko SV, Popova VV. Circulating interleukin-16 in blood of patients with metabolic syndrome and type 2 diabetes mellitus. *Lik Sprava* 2007; 46-9.