AENSI Journals

Advances in Environmental Biology

ISSN-1995-0756 EISSN-1998-1066

Journal home page: http://www.aensiweb.com/aeb.html

Variation of IL-17A and IL-17F Genes in Patients with Breast Cancer in a Population from Southern IRAN (Running title: IL-17 Gene Polymorphisms and Breast Cancer)

[1]Sirous Naeimi, [2]Nasrollah Erfani, [3]Ali M. Ardekani, [2]Abbas Ghaderi

[1]Department of biology, Collage of Science, Tehran Science and Research branch, Islamic Azad University, Tehran, Iran
[2]Cancer immunology group, Shiraz Institute for Cancer Research , School of medicine, Shiraz University of medical sciences, Shiraz, Iran.
[3]National Institute of Genetic engineering and Biotechnology (NIGEB), Tehran, Iran.

ARTICLE INFO

Article history:
Received 15 April 2014
Received in revised form 22 May 2014
Accepted 25 May 2014
Available online 15 June 2014

Key words:
IL-17, Breast Cancer, Polymorphism, Genotype

ABSTRACT

Background: Chronic inflammation plays an important role in the pathogenesis of cancer. The inflammatory response that occurs during the activation of immune responses in most solid tumors may led to tumor cell eradication from one side but help tumor growth from the other side. IL17 is the main cytokine secreted by Th17 cells. This cytokine promotes a localized tissue inflammation by releasing pro inflammatory cytokines and chemokines. The association of gene polymorphism in IL17 A G197A (rs2275913) and IL17F A7488G (rs763780) with disorders such as stomach cancer and lung cancer have been reported.The aim of this study was to evaluate the correlation of these gene polymorphisms with breast cancer in the population of southern Iran. Material and Method: 192 patients and 215 healthy individuals as control participated in this case-control study. PCR-RFLP technique was used to determine the genotypes. The statistical analysis was performed by SPSS software package and the Hardy Weinberg equilibrium was assessed by the Arlequin 3.1. Results: The results indicated that there is no significant difference in the frequency of genotypes and alleles at position IL17 A G197A and IL17F A7488G in patients with breast cancer and the control group (Pv>0.05). Furthermore, we found no significant correlation between the frequency of genotypes and alleles with the clinicopathological factors in the patients. Conclusion: it seems that polymorphism in IL-17A and IL-17 F genes plays no important role in increasing the susceptibility of women to breast cancer in the population of southern Iran.

To Cite This Article: Sirous Naeimi, Nasrollah Erfani, Ali M Ardekani, Abbas Ghaderi, Variation of IL-17A and IL-17F genes in patients with breast cancer in a population from southern Iran. ***Adv. Environ. Biol., 8(9),*** *892-897, 2014*

INTRODUCTION

Breast cancer is the most common malignancy in women and is the second cause of mortality among patients with different types of cancer [1, 2]. Chronic inflammations play important roles in the pathogenesis of autoimmune diseases, allergies and cancers, because inflammation directs the immune system to the damaged tissues or infection sites. Studies have shown that inflammation may simultaneously increase the proliferation, migration and stability of tumor cells through changes in the surrounding environment of tumors [3]. It has also been shown that pro inflammatory cells; Th17, play a dual role in cancer. The pro tumorigenic effects of Th17 are mediated by induction of angiogenesis and usage of inflammatory cells. Th17 cells exert their anti-tumoral effects through indirect induction of the cytotoxic responses of T cells as well as activation of dendritic cells. The main cytokine secreted by Th17 cells is IL17. This pro inflammatory cytokine is the main effector arm of Th17 cells which has been indicated to play roles in autoimmune diseases in humans and mice [4-7].

Members of IL-17 family are involved in immunological diseases and normal immune responses [8]. This family has 6 members, named IL-17A to IL-17F. These pro inflammatory cytokines are a group of homodimers, each made of two 15 KD polypeptide chains joined together by disulfide bonds. In terms of amino acid composition, IL-17A and IL-17F exhibit the most similarities and this similarity can reach 50% [9]. The increase in the expression rate of these cytokines in lung epithelial cells can lead to inflammation of air ducts and mucosal hyperplasia [10]. They also stimulate T cell proliferation and expression of adhesion_molecules. Furthermore, they induce the expression of a wide range of cytokines including IL-6, IL-8, G-CSF, GM-CSF, RANTES and Pr-1 in various cells such as endothelial or epithelial cells. Studies have shown that these cytokines boost the production of nitric oxide and inflammatory cytokines in the inflammation of the synovial

Corresponding Author: Sirous Naeimi, Department of biology, Collage of Science, Tehran Science and Research branch Islamic Azad University, Tehran, Iran
E-mail: Naeimis@kau.ac.ir

space [11, 12]. They also stimulate the osteoklastogenesis and the expression of genes associated with inflammation as well as inducing the expression of ICAM1 in the bronchial epithelial cells [13]. These cytokine is also produced by tumor infiltrating lymphocytes and increases tumorogenicity in the cervical tumor of Nude mice [14, 15].

IL-17A and IL-17F genes are located on chromosome 6 P12. The association of IL17 A G197A polymorphism (rs2275913) and IL17F A7488G polymorphism (rs763780) in the gene of these cytokines have been reported with diseases such as rheumatoid arthritis, colon inflammatory disease, lung cancer and gastric cancer [16-18]. Considering the importance of gene polymorphism in the expression of the IL-17 and the role of genetic factors in cancer development, in present study, we attempted to investigate the relationship between these polymorphisms and the susceptibility of Iranian women to develop breast cancer.

Subjects and methods:

Patients:

The study group included 192 breast cancer patients with a mean age of 49.3± 11.6 who visited Shiraz Namazi and Shahid faghihi hospitals in the years 2007 to 2011 and their breast cancer had been confirmed by pathological studies. The control group consisted of 215 individuals with an average age of 51.8±12.9, who corresponded with the patient group in term of age and sex. Control individuals and their immediate relatives had no history of cancer and autoimmune diseases. Informed consents were obtained from all participants before sampling.

Blood sampling and DNA extraction:

About 1 mL blood was taken from each volunteer and placed in tube containing anticoagulant EDTA (10% solution). For DNA extraction, the saltting-out method was employed. DNA was dissolved in distilled water and DNA purity and concentration was measured by spectrophotometry.

The Polymerase Chain Reaction (PCR):

To determine the genotypes, polymerase chain reaction-restriction length polymorphism (PCR- RFLP) methods were employed. Using specific primers, pieces of DNA containing each locus was amplified. For the position of the IL-17A G197A Forward primer: 5-AAC AAG TAA GAA TGA AAA GAG GAC ATG GT-3, and Reverse primer: 5-CCC CCA ATG AGG TCA TAG AAG AAT C-3 were used (18). For IL-17F A7488G position Forward primer: 5-ACC AAG GCT GCT CTG TTT CT-3 and Reverse primer: 5-GGT AAG GAG TGG CAT TTC TA-3 were used (18) . The PCR reaction mix and thermal programs were almost the same for both positions. The following PCR reaction mix was made for each sample: 11.1 µl distilled water, 1.7 µl PCR buffer (Cinna Gene, Iran), 0.4 µl of $Mgcl_2$, 0.6 ML of dNTP (Cinna Gene, Iran), 0.6 µl Forward Primer, 0.6 µl Reverse Primer, 0.7 µl DNA, and 1.5 µl Taq DNA polymerase(Cinna Gene, Iran). Tubes were placed in thermo cycler with routine PCR program and with the annealing temperature of 65°C and 30 cycles. The amplified IL17 A and IL17 F fragments underwent restriction endonuclease reactions at 37 ° C for 16 hours with *Xag*I (Fermentas, Canada)and *Nla*III (Fermentas, Canada) restriction enzymes respectively. The resulting RFLP products were separated on 2% agarose gel under electrophoresis. The sizes of fragments derived from enzyme digestion are presented in table 1.

Statistical methods:

The data were analyzed using the statistical program SPSS 15 (IBM, USA) and EPI Info 2000 (Georgia,USA). Chi squire (x^2) and Fisher's exact tests were applied to determine the differences in genotype/alleles frequencies. Arlequin 3.1 softwae pakage (19) was used to determine if the distribution of genotypes are in Hardy Weinberg equilibrium.

Results

In this study, the gene polymorphisms at position G197A (rs2275913) in IL17A gene and A7488G (rs763780) in IL17F gene were studied among 192 patients with breast cancer and 215 women as controls. The clinico-pathological information of the patients is shown in table 2. 88.9 %of the patients had infiltrative ductal carcinoma (IDC) and 69.1 % were in the stage II of the disease. The distribution of studied genotypes was confirmed to be in Hardy Weinberg equilibrium.

Table 3 illustrates the frequencies of genotypes and alleles at G197A position in IL17A gene as well as A7488G locus in IL17 F gene. The frequency of GG, GA, and AA genotypes among patients and control group at the position G197A in IL17A gene were 47.9% versus 41.9%, 41.7% versus 47.4%, and 10.4% versus 10.7%, respectively. The frequency of G and A alleles among patients and controls was respectively 68.75% versus 65.6%; and 31.25% versus 34.4%.

In addition, the frequencies of AA, AG and GG genotypes among patients and control group at position A7488G in IL17 F gene observed to be 74.5% versus 72.1%, 25% versus 26%, and 0.5% versus 1.9%,

respectively. The frequency of allele A was 86.9% versus 85.1% and that of allele G was 13.1% versus 14.9%, respectively. Statistical analysis indicated that there is no significant difference between the distribution of various genotypes and alleles among patients with breast cancer and control group (P=0.44 and 0.44 for genotypes and allele respectively, Table 3).

No significant correlation was found between the frequency of inherited genotypes and clinical-pathological factors of the disease including tumors histology, tumor stage, the involvement of blood and lymphatic vessels by the tumor cells, tumor size, tumor grade, draining lymph node metastasis, the expression of estrogen and progesterone receptors and prognosis of tumors based on Nottingham index.

Discussion and Conclusion:

Breast cancer is one of the most common cancers in females worldwide [20]. In recent years, several studies have identified some of the genetic indicators involved in cancer development. Among these genes, those related to cytokines and chemokines are of special importance, since they not only have effects on the anti-tumor immune responces but also may affect the progression of tumor.

Th17 lymphocytes play a role in regulation of the immune system and localized tissue inflammation. They carry out these important functions through the production and secretion of IL-17 cytokine. These lymphocytes are involved in angiogenesis and tumor progression via stimulation the production of a wide range of proangiogiotic factors. On the other hand, these cells play a role in the inhibition of tumor growth by augmenting cytotoxic responses of NK cells and CTLs (21, 22). In the present study the gene polymorphisms in IL17 A G197A (rs2275913) and IL17F (A7488G (rs763780) were investigated in patients with breast cancer compared with the healthy control group. The results indicated that the frequencies of investigated genotype and alleles in IL17A and IL17F genes are not significantly different in breast cancer and the control group. Similarly, there was no significant correlation between the frequency of inherited genotypes and clinical-pathological factors of disease in breast cancer patients.

Spinoza *et al*. in a reporter gene assay showed that the presence A allele at position 197 in IL17A gene induces more Losifraz activity than the G allele at this position. Furthermore, this group indicated that A allele has more affinity to transcribing factor NFAT and exerts its effects through binding of NFAT [23]. The replacement of guanine to adenine at position 7488 in the exon 3 of IL-17F geneleds to a codon change in DNA sequence followed by the amino acid change in the nascent protein. This change leads to substitution of histidine (CAT) to arginine (CGT) in the protein [24]. In a study by Wang *et al*. on the Chinese patients with breast cancer, the frequency of AA genotype at position 197 in IL17A (rs2275913) was observed to be increased in patients compared with the control group. In contrast, such a difference was not observed in the case of IL17F A7488G polymorphism (rs 763780) [25] . Spinoza *et al*. showed that people who inherit IL17 197 A allele have the higher risk to develpoe acute GVHD. They indicated that the production of IL-17 in individuals with 197A allele is much greater than those carrying 197G [23] .Tahara *et al*. examined the possible correlation of gastric cancer with gene variant of IL-17A 197G/A (rs2275913) and IL -17F A7488G (rs763780) .The findings suggested that 197A allele is associated with the progression of gastric cancer. Furthermore, the frequency of 197AA homozygous genotype in IL-17A observed to be higher among gastric cancer patients than healthy individuals [26]. In another study, this group investigated the association of polymorphisms in IL-17A and IL17F genes on C_PG Island Hyper Methylation (CIHM) in gastric cancer. The results indicated that the probability of occurrence of (CIHM;which is one of the contributing factors in stomach cancer) is higher in people who have GA and GG genotype than those with AA genotype [27].Wu *et al* found that the probability of gastrointestinal cancer in people with GG genotype at position G7488A in IL-17F gene is higher than those with AA genotype. This group however did not find association between gastric cancer and IL-17A 197 polymorphism [18]. In another study by Zhou B *et al*, association of IL-17A 197G/A and IL -17F A7488G gene polymorphisms with bladder cancer were examined. This group found differences in the frequencies AA genotype and A allele in IL17 A [28].

Despite the observed association between the examined polymorphisms and stomach, bladder and breast cancers in other studies, the results of the present study showed no significant association between polymorphisms of IL17 A, and IL17 F with susceptibility to breast cancer in the population of southern Iran. We also did not find the association between the inherited genotypes with the clinicopathological characteristics in the patients. Inconsistent findings may be related to the sample size, differences in the molecular pathology of different cancers and also may come from the genetic background of sample population. The minor allele frequency (MAF) of IL17A A197G and IL17F A7488G polymorphisms in our population was 0.33 and 0.14 respectively. The figures were 0.51 and 0.21 in Chinese population [26]. In Japanese population MAF of IL17A A197G polymorphism was 0.42 [17]. In another study this figure in chine's population with breast cancer was 0.39 [25] and in patient with cervical cancer was 0.50 [29].

Our data conclusively indicated that the G197A polymorphism in IL17 A gene (rs2275913) and A7488G polymorphism in IL17 F (rs763780) are not associated with the susceptibility to, or the progression of breast cancer in southern Iran.

ACKNOWLEDGEMENTS

This work was financially supported in part by the grant from Shiraz institute for Cancer research, School of medicine, Shiraz University of medical sciences, Shiraz, Iran .Grant Number: ICR-100-500.

Table 1: Primers, annealing temperatures, restriction enzymes and the size of RFLP products for IL17A and F genotyping.

Single nucleotide polymorphism	Annealing Temperature	Restriction Endonuclease Enzyme	Recognition Site	Fragments
IL-17A G197A rs2275913	65	XagI	5'...CCTNN↓NNNAGG...3' 3´…GGANNN↑NNTCC…5´	GG (68 and 34 bp GA(102, 68 and 34 bp) AA (102 bp)
IL-17F A7488G rs763780	65	Nla III	5'...CATG↓...3' 3´…↑GTAC …5´	AA (63 and 80 bp) AG (143, 80 and 63bp) GG (143 bp)

Table 2: Clinicopathological characteristics of the patients with breast cancer.

Clinicopathological characteristic	No. out of 192	Statistics
Age (years)	192	Mean ± SD: 49.3 ± 11.6 , Minimum: 26, Maximum: 82
Tumor type	189	IDC-NOS (%88.9), MC (%4.2), Met.C (%1.6), Other-IDC (%2.6), ISDC (%1.6), ILC (%1.1)
TNM stage	157	Stage I: %17.8, Stage II: %69.1, Stage III:% 11.8, Stage IV:% 1.3
Lymph node (LN) status	155	Free:% 48.4, Involved:% 51.6
Lymphovascular invasion (LVI)	132	Negative: 24.2%, Positive: 75.8%
Tumor size (cm)	143	Size ≤2: 32.2% 2< Size ≤ 5: 59.4% Size >5: 8.4%
Histological grade	114	Grade 1(Well Differentiated): 34.5% Grade 2 (Moderately Differentiated): 52.2% Grade 3 (Poorly Differentiated): 13.3%
Distant metastases at the time of diagnosis	153	Negative: 98.7% Positive: 1.3%
ER expression	131	Negative: 42% Positive: 58%
PR expression	131	Negative: 41.2% Positive: 58.8%
Nottingham Prognostic Index	110	NPI ≤ 3.4(Good prognosis):22.9% 3.4 < NPI ≤ 5.4, (Moderate prognosis): 54.3% NPI > 5.4, (Poor prognosis):22.9%

Table 3: The frequencies of genotypes and alleles of IL-17A G197A polymorphism (rs2275913) and IL-17F A7488G polymorphism (rs763780) in patients with breast cancer and healthy control subjects.

Position			Patients 192	Controls 215	Pv
IL-17A G197A rs2275913	Genotypes	GG	92(47.9 %)	90 (41.9%)	0.45
		GA	80 (41.7%)	102 (47.4%)	
		AA	20 (10.4%)	23(10.7%)	
	Alleles	G	264 (68.75%)	282(65.6%)	0.33
		A	120 (31.25%)	148 (34.4%)	
IL-17F A7488G rs763780	Genotypes	AA	143 (74.5%)	155(72.1%)	0.44
		AG	48 (25%)	56(26%)	
		GG	1(0.5%)	4(1.9%)	
	Alleles	A	334 (86.9%)	366 (85.1%)	0.44
		G	50 (13.1%)	64(14.9%).	

REFERENCES

[1] Vogelstein, B., KW. Kinzler, 2004. Cancer genes and the pathways they control. Nat Med. Aug, 10(8):7 89-99. PubMed PMID: 15286780. Epub 2004/08/03. eng.

[2] Hanahan, D., RA. Weinberg,2000. The hallmarks of cancer. Cell. 7., 100(1): 57-70. PubMed PMID: 10647931. Epub 2000/01/27. eng.

[3] Zou, W., NP. Restifo.,2010. T(H)17 cells in tumour immunity and immunotherapy. Nat Rev Immunol. Apr., 10(4): 248-56. PubMed PMID: 20336152. Pubmed Central PMCID: 3242804. Epub 2010/03/26. eng.

[4] Aggarwal, S., AL. Gurney, 2002. IL-17: prototype member of an emerging cytokine family. J Leukoc Biol., 71(1): 1-8. PubMed PMID: 11781375. Epub 2002/01/10. eng.

[5] Gaffen, SL., 2004. Biology of recently discovered cytokines: interleukin-17--a unique inflammatory cytokine with roles in bone biology and arthritis. Arthritis Res Ther, 6(6): 240-7. PubMed PMID: 15535837. Pubmed Central PMCID: 1064872. Epub 2004/11/13. eng.
[6] Huang, SH., S. Frydas, D. Kempuraj, RC. Barbacane, A. Grilli, W. Boucher, 2004. Interleukin-17 and the interleukin-17 family member network. Allergy Asthma Proc., 25(1): 17-21. PubMed PMID: 15055556. Epub 2004/04/02. eng.
[7] Kolls, JK., A. Linden, 2004. Interleukin-17 family members and inflammation. Immunity, 21(4): 467-76. PubMed PMID: 15485625. Epub 2004/10/16. eng.
[8] Fossiez, F., O. Djossou, P. Chomarat, L. Flores-Romo, S. Ait-Yahia, C. Maat, 1996. T cell interleukin-17 induces stromal cells to produce proinflammatory and hematopoietic cytokines. J Exp Med. 1; 183(6): 2593-603. PubMed PMID: 8676080. Pubmed Central PMCID: 2192621. Epub 1996/06/01. eng.
[9] Moseley, TA., DR. Haudenschild, L. Rose, AH. Reddi, 2003. Interleukin-17 family and IL-17 receptors. Cytokine Growth Factor Rev., 14(2): 155-74. PubMed PMID: 12651226. Epub 2003/03/26. eng.
[10] Yang, XO., SH. Chang, H. Park, R. Nurieva, B. Shah, L. Acero, 2008. Regulation of inflammatory responses by IL-17F. J Exp Med., 12; 205(5): 1063-75. PubMed PMID: 18411338. Pubmed Central PMCID: 2373839. Epub 2008/04/16. eng.
[11] Attur, MG., RN. Patel, SB. Abramson, AR. Amin, 1997. Interleukin-17 up-regulation of nitric oxide production in human osteoarthritis cartilage. Arthritis Rheum, 40(6): 1050-3. PubMed PMID: 9182915. Epub 1997/06/01. eng.
[12] Amin, AR., SB. Abramson, 1998. The role of nitric oxide in articular cartilage breakdown in osteoarthritis. Curr Opin Rheumatol, 10(3): 263-8. PubMed PMID: 9608331. Epub 1998/06/03. eng.
[13] Kawaguchi, M., F. Kokubu, H. Kuga, T. Tomita, S. Matsukura, H. Hoshino, 1999. [Effect of IL-17 on ICAM-1 expression of human bronchial epithelial cells, NCI-H 292]. Arerugi, 48(10): 1184-7. PubMed PMID: 10554406. Epub 1999/11/11. jpn.
[14] Tartour, E., F. Fossiez, I. Joyeux, A. Galinha, A. Gey, E. Claret, 1999. Interleukin 17, a T-cell-derived cytokine, promotes tumorigenicity of human cervical tumors in nude mice. Cancer Res., 1; 59(15): 3698-704. PubMed PMID: 10446984. Epub 1999/08/14. eng.
[15] Fridman, WH., E. Tartour, 1998. Macrophage- and lymphocyte-produced Th1 and Th2 cytokines in the tumour microenvironment. Res Immunol, 149(7-8): 651-3. PubMed PMID: 9851518. Epub 1998/12/16. eng.
[16] Nordang, GB., MK. Viken, JE. Hollis-Moffatt, TR. Merriman, OT. Forre, K. Helgetveit, 2009. Association analysis of the interleukin 17A gene in Caucasian rheumatoid arthritis patients from Norway and New Zealand. Rheumatology (Oxford), 48(4): 367-70. PubMed PMID: 19208686. Epub 2009/02/12. eng.
[17] Arisawa, T., T. Tahara, T. Shibata, M. Nagasaka, M. Nakamura, Y. Kamiya, 2008. The influence of polymorphisms of interleukin-17A and interleukin-17F genes on the susceptibility to ulcerative colitis. J Clin Immunol, 28(1): 44-9. PubMed PMID: 17828618. Epub 2007/09/11. eng.
[18] Wu, X., Z. Zeng, B. Chen, J. Yu, L. Xue, Y. Hao, 2010. Association between polymorphisms in interleukin-17A and interleukin-17F genes and risks of gastric cancer. Int J Cancer, 1; 127(1): 86-92. PubMed PMID: 19904747. Epub 2009/11/12. eng.
[19] Laurent Excoffier, Guillaume Laval, S. Schneider, 2005. How to cite Arlequin 3.1 An integrated software package for population genetics data analysis Evolutionary Bioinformatics Online, 1: 47-50.
[20] Parkin, DM., P. Pisani, J. Ferlay, 1999. Global cancer statistics. CA: a cancer journal for clinicians, 49(1): 33-64, 1. PubMed PMID: 10200776. Epub 1999/04/14. eng.
[21] Hinrichs, CS., A. Kaiser, CM. Paulos, L. Cassard, L. Sanchez-Perez, B. Heemskerk, 2009. Type 17 CD8+ T cells display enhanced antitumor immunity. Blood, 16; 114(3): 596-9. PubMed PMID: 19471017. Pubmed Central PMCID: 2713473. Epub 2009/05/28. eng.
[22] Maniati, E., R. Soper, T. Hagemann, 2010. Up for Mischief? IL-17/Th17 in the tumour microenvironment. Oncogene, 21; 29(42): 5653-62. PubMed PMID: 20729908. Pubmed Central PMCID: 2962667. Epub 2010/08/24. eng.
[23] Espinoza, JL., A. Takami, K. Nakata, M. Onizuka, T. Kawase, H. Akiyama, 2011. A genetic variant in the IL-17 promoter is functionally associated with acute graft-versus-host disease after unrelated bone marrow transplantation. PLoS One., 6(10): e26229. PubMed PMID: 22028838. Pubmed Central PMCID: 3197629. Epub 2011/10/27. eng.
[24] Paradowska-Gorycka, A., E. Wojtecka-Lukasik, J. Trefler, B. Wojciechowska, JK. Lacki, S. Maslinski, 2010. Association between IL-17F gene polymorphisms and susceptibility to and severity of rheumatoid arthritis (RA). Scandinavian journal of immunology, 72(2): 134-41. PubMed PMID: 20618772.
[25] Wang, L., Y. Jiang, Y. Zhang, Y. Wang, S. Huang, Z. Wang, 2012. Association analysis of IL-17A and IL-17F polymorphisms in Chinese Han women with breast cancer. PLoS One., 7(3):e34400. PubMed PMID: 22461912. Pubmed Central PMCID: 3312906. Epub 2012/03/31. eng.

[26] Shibata, T., T. Tahara, I. Hirata, T. Arisawa, 2009. Genetic polymorphism of interleukin-17A and -17F genes in gastric carcinogenesis. Hum Immunol, 70(7): 547-51. PubMed PMID: 19414056. Epub 2009/05/06. eng.
[27] Tahara, T., T. Shibata, M. Nakamura, H. Yamashita, D. Yoshioka, M. Okubo, 2010. Association between IL-17A, -17F and MIF polymorphisms predispose to CpG island hyper-methylation in gastric cancer. Int J Mol Med., 25(3): 471-7. PubMed PMID: 20127054. Epub 2010/02/04. eng.
[28] Zhou, B., P. Zhang, Y. Wang, S. Shi, K. Zhang, H. Liao, 2012. Interleukin-17 gene polymorphisms are associated with bladder cancer in a Chinese Han population. Mol Carcinog, 12. PubMed PMID: 22692973. Epub 2012/06/14. Eng.
[29] Quan, Y., B. Zhou, Y. Wang, R. Duan, K. Wang, Q. Gao, 2012. Association between IL17 polymorphisms and risk of cervical cancer in Chinese women. Clin Dev Immunol, 2012: 258293. PubMed PMID: 23049595. Pubmed Central PMCID: PMC3463183. Epub 2012/10/11. eng.