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Original Article

Association between interleukin-18 genetic polymorphisms and development of acute pancreatitis risk in a Chinese population

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Abstract: Here, we conducted a case-control study to investigate the association between two promoter SNPs in *IL-18*, rs1946518 and rs187238 genetic variations and acute pancreatitis susceptibility in a Chinese population. This study comprised of 172 patients with acute pancreatitis and 236 control subjects. The *IL-18* genotyping for rs1946518 and rs187238 polymorphic sites was determined using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). As confirmed by chi-square tests, acute pancreatitis patients and healthy control subjects differed significantly in genotype frequencies at *IL-18* rs187238 (χ^2=10.52, P=0.005). The multiple logistic regression analysis revealed that the CC genotype of *IL-18* rs187238 was significantly associated with the acute pancreatitis susceptibility in this population (adjusted OR=3.01, 95% CI=1.43-6.49), when compared with the healthy control subjects. Additionally, the C allele of *IL-18* rs187238 was more significantly correlated with the risk of acute pancreatitis susceptibility as compared to the G allele (adjusted OR=1.63, 95% CI=1.19-2.23). However, no significant relationship was observed between *IL-18* rs1946518 and risk of acute pancreatitis susceptibility. In conclusion, we suggested that the *IL-18* rs187238 gene polymorphisms may influence the susceptibility to acute pancreatitis in a Chinese population.

Keywords: *IL-18*, rs1946518, rs187238, polymorphism, acute pancreatitis

Introduction

Acute pancreatitis is an acute inflammatory condition of the pancreatic gland that involves a systemic inflammatory response [1, 2]. Acute pancreatitis is attributed to the outcome of disequilibrium between inflammatory mediators and anti-inflammatory mediators, and is caused by an excess of pro-inflammatory mediators [3, 4]. Acute pancreatitis is related with high mortality rate, and it is estimated that the mortality of this disease is about 10%-25% based on the severity and infection condition [5]. Even though improvements in early detection have decreased the mortality rates of acute pancreatitis in recent years, prevention of acute pancreatitis is always a main public health concern. The pathogenesis of acute pancreatitis is associated with many environmental and lifestyle factors, such as gallstones, long-term alcohol drinking, pancreas trauma, obstructive pancreatic duct, bacterial or viral infections, hypercalcemia or hyperlipidemia as well as acute embolism or obstruction of pancreas arteries or veins [6-8]. It is reported that 60%-80% of the acute pancreatitis could be attributed to biliary tract disease and alcoholism. But the 10%-30% of etiology of the acute pancreatitis remains unknown [9]. Not all individuals suffering from risk factors of acute pancreatitis would develop this disease, which suggests that genetic factors may contribute to the pathogenesis of acute pancreatitis. Thus, proper understanding of the molecular pathogenesis for acute pancreatitis is highly imperative for the development of diagnostic/prognostic markers and also for treatment strategies.

Interleukin-18 (*IL-18*), an 18-kDa cytokine, belongs to the interleukin-1 (*IL-1*) superfamily [10]. *IL-18* is a pleiotropic cytokine, and is mainly produced by the activation of mononuclear macrophages. *IL-18* induces the production of IFN-γ, and participates into pathological pro-

Table 1. Primers, restriction enzymes and PCR products of IL-18 rs1946518 and rs187238

IL-18 gene	Primers (5'-3')	Restriction enzymes	PCR products	Digested fragments
rs1946518	Forward: CCCTCTCCCCAAGCTTACTT Reverse: TTCAGTGGAACAGGAGTCCA	MseI	171 bp	CC: 171 bp CA: 171 bp, 101 bp and 70 bp AA: 101 bp and 70 bp
rs187238	Forward: TTGTAACATTGTAGGAATTACC Reverse: ATGTAATATCACTATTTTATGAGA	EcoRI	131 bp	GG: 107 bp and 24 bp GC: 131 bp, 107 bp and 24 bp CC: 131 bp

cess of various diseases [10]. Genetic polymorphisms change the structure and quantity of the gene product; ultimately affect the function of the product and contributing to the risk of disease susceptibility [11]. Previous studies have demonstrated that the single nucleotide polymorphisms of *IL-18*, such as -607C/A (rs1946518) and -137G/C (rs187238), are associated with alteration of the activity and expression of *IL-18* [12-15]. Currently, no previous studies have reported the role of IL-18 genetic polymorphisms in the risk of acute pancreatitis susceptibility. Therefore, we conducted a case-control study to investigate the association between two promoter SNPs in *IL-18* (rs1946518 and rs187238) genetic variations and acute pancreatitis susceptibility in a Chinese population.

Materials and methods

Subjects

A hospital based case-control design was taken in this study. This study comprised of 172 patients with acute pancreatitis and 236 control subjects. The 172 patients with acute pancreatitis were newly diagnosed and consecutively recruited from the Guizhou Provincial People's Hospital during the time period between March 2013 and May 2015. The diagnosis criteria of acute pancreatitis was according to the CT scan verification of pancreatitis, clinical manifestation of abdominal pain or abdominal localizing signs, and elevated amylase levels by at least 3 times than the upper limit of normal. Patients with a history of malignant cancers, endocrine diseases and serious infection diseases, as well as end-stage liver and kidney diseases were excluded from this study.

The healthy controls were recruited from among individuals who visit the outpatient clinics in the Guizhou Provincial People's Hospital. All the included control subjects confirmed to be free of acute pancreatitis by CT scan examination. Moreover, the exclusion criteria for control subjects were those with digestive system diseases, acute and chronic infection diseases, endocrine diseases, malignant tumors as well as end-stage liver and kidney diseases.

A detailed questionnaire was filled for each case and control by a trained interviewer. All the information in terms of demographic and lifestyle factors was obtained with the help of the questionnaire form filled by a trained personnel. The demographic and lifestyle factors comprised of age, gender, body mass index (BMI), tobacco smoking and alcohol consumption, as well as family history of acute pancreatitis. The clinical data were collected from medical records, including total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (HDL-c) and high-density lipoprotein cholesterol (LDL-c). The performance of this study obtained the permission of the Institutional Review Board of Guizhou Provincial People's Hospital. A written informed consent was gained from each participant prior to recruitment. The ethical standards adopted were based on the requirements of the declaration of Helsinki.

Genotyping analysis

Each study subject was asked to provide five peripheral blood samples, and then the blood samples were stored in tubes with 5% EDTA and kept at -20°C until using. The Qiagen DNA Blood Mini Kit (Qiagen, Valencia, CA, USA) was employed to extract the DNA from peripheral blood samples, according to the manufacture's recommendation. The *IL-18* genotyping for rs1946518 and rs187238 polymorphic sites was determined using polymerase chain reaction-restriction fragment length polymorphism

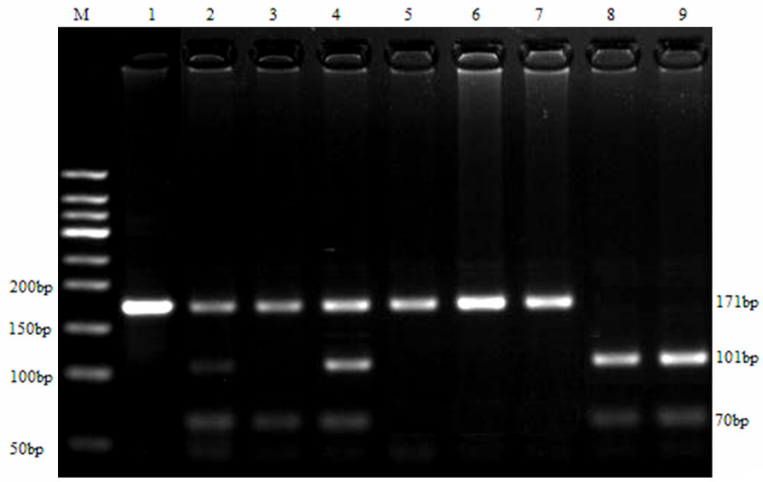

Figure 1. Agarose gel electrophoresis images for IL-18 rs1946518.

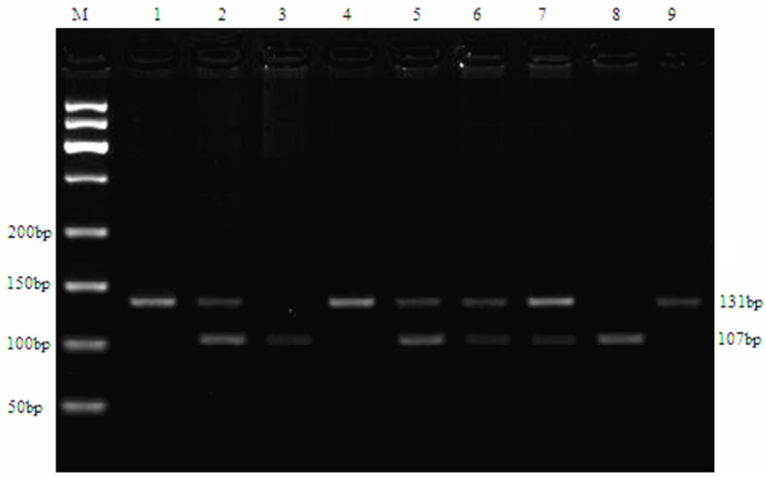

Figure 2. Agarose gel electrophoresis images for IL-18 rs187238.

(PCR-RFLP). DNA samples were amplified using two different primer pairs specific for the two polymorphic regions of *IL-18* gene. The primer sequences for polymorphic sites, restriction enzymes and digested fragments for PCR products were summarized in **Table 1**. PCR reaction was performed in a 25 μl reaction mixture, including 18.5 μl of ddH_2O, 2.0 μl of DNA template, 0.5 μl of forward primer, 0.5 μl of reverse primer, 0.5 μl of dNTP mixtures, 2.5 μl 10×PCR buffer solution and 0.5 μl TaqDNA polymerase. The PCR conditions was carried out for initial denaturation at 95°C for 5 minutes, followed by 35 cycles of denaturation at 94°C for 30 seconds, annealing at 63.1°C for 30 seconds, extension at 72°C for 30 seconds, and a final elongation of 7 mins at 72°C. Then the product was stored at 4°C. The resulted fragments were electrophoresized on 2% agarose gel stained with ethidium bromide to determine the genotypes of the subjects for the polymorphic sites (**Figures 1** and **2**).

Statistical analysis

Variances of demographic and lifestyle data between acute pancreatitis patients and control subjects were determined using the chi-square tests (χ^2 test) or student *t* test. The Hardy-Weinberg Equilibrium (HWE) for any deviation from expected allele frequencies were tested by using χ^2 test. Univariate and multivariate logistic regression analyses were taken to analyze the association between *IL-18* rs1946518 and rs187238 polymorphisms and development of acute pancreatitis. The minor allele frequency (MAF) of *IL-18* rs1946518 and rs187238 were compared with those in National Center of Biotechnology Information (https://www.ncbi.nlm.nih.gov/snp). The results were determined using odd ratio (OR) and 95% confidence interval (CI). The multiple logistic regression analysis was conducted for confounding factors adjustment. Univariate and multivariate logistic regression analyses were done by using SPSS version 20.0 (Armonk, NY: IBM Corp, USA). A *p*-value <0.05 at 95% confidence interval (CI) was taken as statistically significant.

Results

The demographic, lifestyle and clinical characteristics of acute pancreatitis patients and control subjects are summarized in **Table 2**. The acute pancreatitis patients and control subjects were comparable in respect to tobacco smoking (χ^2=0.44, P=0.51) and family history of acute pancreatitis (χ^2=1.34, P=0.25). In comparison to the control subjects, acute pancreatitis patients were more likely to have older age (t=2.37, P=0.009), be males (χ^2=4.55,

Table 2. Demographic and lifestyle as well as clinical characteristics of study subjects

Variables	Patients N=172	%	Controls N=236	%	χ^2 test or t test	*P* value
Age, years	63.52±9.22		61.42±8.54		2.37	0.009
Gender						
Female	62	36.05	110	46.61		
Male	110	63.95	126	53.39	4.55	0.03
BMI, kg/m^2	25.56±3.15		24.25±2.76		4.46	<0.05
Tobacco smoking						
No	106	61.63	153	64.83		
Yes	66	38.37	83	35.17	0.44	0.51
Alcohol consumption						
No	116	67.44	208	88.14		
Yes	56	32.56	28	11.86	26.06	<0.05
Family history of acute pancreatitis						
No	164	95.35	230	97.46		
Yes	8	4.65	6	2.54	1.34	0.25
Gallstones						
No	111	64.53	228	96.61		
Yes	61	35.47	8	3.39	72.84	<0.05
TC, mmol/L	5.12±1.24		4.44±1.27		5.39	<0.05
TG, mmol/L	1.86±1.05		1.55±0.97		3.08	0.001
LDL-c, mmol/L	2.93±1.24		2.71±1.15		1.85	0.03
HDL-c, mmol/L	1.31±0.53		1.42±0.47		2.21	0.01

P=0.03), have a habit of alcohol consumption (χ^2=26.06, P<0.05), have a history of gallstones (χ^2=72.84, P<0.05), and have higher levels of TC (t=5.39, P<0.05), TG (t=3.08, P=0.001), LDL-c (t=1.85, P=0.03) and HDL-c (t=2.21, P=0.01).

The genotype distributions of *IL-18* rs1946518 and rs187238 are presented in **Table 3**. As confirmed by chi-square tests, acute pancreatitis patients and healthy control subjects differed significantly in genotype frequencies at *IL-18* rs187238 (χ^2=10.52, P=0.005), whereas no significant difference was shown between *IL-18* rs1946518 and acute pancreatitis susceptibility (χ^2=2.69, P=0.26). The genotype frequencies of *IL-18* rs1946518 and rs187238 did not deviate from HWE in both patients (*P* values were 0.12 and 0.05 for rs1946518 and rs187238, respectively) and controls (*P* values were 0.14 and 0.99 for rs1946518 and rs187238, respectively). Additionally, the MAF values of rs1946518 and rs187238 in controls were similar with those in database from National Center of Biotechnology Information.

The relationship between *IL-18* rs1946518 and rs187238 genetic polymorphisms and acute pancreatitis risk is shown in **Table 4**. The multiple logistic regression analysis revealed that the CC genotype of *IL-18* rs187238 was significantly associated with the acute pancreatitis susceptibility in this population (adjusted OR=3.01, 95% CI=1.43-6.49), when compared with the healthy control subjects. Additionally, the C allele of *IL-18* rs187238 was more significantly correlated with the risk of acute pancreatitis susceptibility as compared to the G allele (adjusted OR=1.63, 95% CI=1.19-2.23). However, no significant relationship was observed between *IL-18* rs1946518 and risk of acute pancreatitis susceptibility.

Moreover, we carried out gene-environmental interaction between *IL-18* rs1946518 and rs187238 gene polymorphisms and demographic and lifestyle as well as clinical characteristics in the development of acute pancreatitis. However, we did not find any gene-environmental interaction between them (*P*>0.05).

Table 3. Genotype distributions of IL-18 rs1946518 and rs187238 of the study groups

IL-18	Patients N=172	%	Controls N=236	%	χ^2 test	*P* value	P for HWE		MAF	
							Patients	Controls	Controls	Database
rs1946518										
CC	57	33.14	95	40.25						
CA	75	43.60	98	41.53						
AA	40	23.26	43	18.22	2.69	0.26	0.12	0.05	0.3898	0.4079
rs187238										
GG	76	44.19	132	55.93						
GC	70	40.70	89	37.71						
CC	26	15.12	15	6.36	10.52	0.005	0.14	0.99	0.2521	0.2127

HWE: Hardy-Weinberg equilibrium; MAF: minor allele frequency.

Table 4. Relationship between IL-18 rs1946518 and rs187238 genetic polymorphisms and acute pancreatitis risk

IL-18	Patients N=172	%	Controls N=236	%	OR (95% CI)[1]	*P* value
rs1946518						
CC	57	33.14	95	40.25	1.0 (Ref.)	-
CA	75	43.60	98	41.53	1.28 (0.80-2.04)	0.28
AA	40	23.26	43	18.22	1.55 (0.87-2.76)	0.11
Allele						
C	189	54.94	288	61.02	1.0 (Ref.)	-
A	155	45.06	184	38.98	1.28 (0.96-1.72)	0.08
rs187238						
GG	76	44.19	132	55.93	1.0 (Ref.)	-
GC	70	40.70	89	37.71	1.37 (0.88-2.13)	0.15
CC	26	15.12	15	6.36	3.01 (1.43-6.49)	0.001
Allele						
G	222	64.53	353	74.79	1.0 (Ref.)	-
C	122	35.47	119	25.21	1.63 (1.19-2.23)	0.002

[1]Adjusted for age, gender, BMI, alcohol consumption, gallstones, TC, TG, LDL-c and HDL-c. OR, odds ratio; CI, confidence interval.

Discussion

Acute pancreatitis is the one of the leading causes of death, and is a severe public health problem worldwide. So far, the identified factors correlated with acute pancreatitis were environment, ethnicity, family history and genetic mutation. Currently, many studies have shown that chronic inflammation could be a potential role in the development of acute pancreatitis, such as IL-10, IL-1β, IL-8 and IL-6 [16-19]. The continuous condition of inflammation produces chronic damage promoting development and progression of acute pancreatitis. In the present study, we firstly estimated the relationship between *IL-18* rs1946518 and rs187238 gene polymorphisms and the development of acute pancreatitis in a Chinese population, and we observed that the CC genotype and C allele of *IL-18* rs187238 were associated with an increased risk of acute pancreatitis compared to the wide-type genotype.

The *IL-18* gene is located on chromosome 11q22.2-q22.3, including six exons and five introns. Previous studies have reported that IL-18 has pleiotropic efficacy in activating natural killer cell cytotoxic effect and enhancing Th1 immune response mainly by stimulating the expression of interferon-γ and tumor necrosis factor-α, therefore resulting in the elimination of normal cells in vivo [12, 20]. It is reported that genetic polymorphisms could influence the expression and function of *IL-18* [21]. Many previous studies have revealed that *IL-18* gene polymorphisms could affect the susceptibility to several kinds of diseases, such as rheumatoid arthritis, papillary thyroid cancer, tuberculosis, hepatitis B virus related liver disease and Crohn's disease [15, 22-25]. Angelo et al. carried out a study with 90 rheumatoid arthritis and 186 healthy individuals, and they reported that *IL-18* polymorphism contributed to the rheumatoid arthritis susceptibility [22]. Chung et al. carried a study in a Korean population, and revealed that *IL-18* rs549908, rs360717, and rs187238 polymorphisms may play an important role in

the development of papillary thyroid cancer [23]. Zhou et al. carried out a study with 407 tuberculosis patients and 469 healthy volunteers in China, and reported that *IL-18* rs187238 polymorphism contributed to tuberculosis susceptibility in Chinese Han population [24]. Lu et al. carried out a study in a Chinese population, and indicated that the *IL-18* rs187238 may be an independently protective factor for HBV-related disease [15]. Gao carried out a meta-analysis with seven case-control studies, and reported that *IL-18* rs1946518 and rs187238 polymorphisms may play an important role in the susceptibility to Crohn's disease [25].

For the association between *IL-18* and acute pancreatitis risk, several studies have reported the relationship between *IL-18* levels and development of acute pancreatitis [26-29]. Janiak et al. carried out a study with 32 patients and 30 healthy controls, and revealed that serum *IL-18* level was correlated with an increased risk of the initial phase of acute pancreatitis and prognosis of this disease [26]. Liang et al. done a study with 87 acute pancreatitis patients and 50 healthy subjects, and reported that serum levels of IL-18 positively correlated the severity of liver damage in the acute pancreatitis patients [27]. Pastor et al. reported that IL-18 expression could be a biomarker for monitoring the severity of acute pancreatitis in rats [28]. Meng et al. revealed that the increased in IL-18 expression could influence the deterrior inflammation in the pancreas [29]. However, no study reports the relationship between *IL-18* genetic polymorphisms and development of acute pancreatitis. In our study, we firstly reported the CC genotype and C allele rs187238 are associated with acute pancreatitis risk in a Chinese population. The molecular mechanisms underlying pathogenesis of acute pancreatitis have still not been entirely elucidated. The efforts to recognize molecular markers for early detection of acute pancreatitis as well as personalize both patient prognosis and therapy are of critical clinical significance.

Two limitations should be mentioned in the present study. First, selection bias may be present, as all patients and control subjects were recruited from one hospital. However, genotype distributions of *IL-18* rs1946518 and rs187238 confirmed with Hardy-Weinberg equilibrium, suggesting that the study subjects could good represent the general population. Second, other cytokine genes which may have interacted with the *IL-18* gene were not included in our statistical analysis. Thus, further studies with large sample size are required to confirm the finding of our study.

In conclusion, we suggested that the *IL-18* rs187238 gene polymorphisms may influence the susceptibility to acute pancreatitis in a Chinese population. Further studies are greatly needed to confirm the results of our findings.

Disclosure of conflict of interest

None.

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References

[1] Ozhan G, Sari FM, Vefai M, Yanar HT, Alpertunga B. Acute pancreatitis is associated with Ser-608Leu iNOS polymorphism. Folia Biologica 2012; 5: 256-60.

[2] Powell JJ, Fearon KC, Siriwardena AK, Ross JA. Evidence against a role for polymorphisms at tumor necrosis factor, interleukin-1 and interleukin-1 receptor antagonist gene loci in the regulation of disease severity in acute pancreatitis. Surgery 2001; 129: 633-40.

[3] Goldie AS, Fearon KC, Ross JA, Barclay GR, Jackson RE, Grant IS, Ramsay G, Blyth AS, Howie JC. Natural cytokine antagonists and endogenous antiendotoxin core antibodies in sepsis syndrome. The Sepsis Intervention Group. JAMA 1995; 274: 172-7.

[4] He C, Zhang L, Shi W, Liang X, Ye Z, Zhang B, Liu S. Coupled plasma filtration adsorption combined with continuous veno-venous hemofiltration treatment in patients with severe acute pancreatitis. J Clin Gastroenterol 2013; 47: 62-8.

[5] Yousaf M, McCallion K, Diamond T. Management of severe acute pancreatitis. Br J Surg 2003; 90: 407-420.

[6] Lankisch PG, Apte M, Banks PA. Acute pancreatitis. Lancet 2015; 386: 85-96.

[7] Yuhara H, Ogawa M, Kawaguchi Y, Igarashi M, Mine T. Smoking and risk for acute pancreatitis: a systematic review and meta-analysis. Pancreas 2014; 43: 1201-7.

[8] Kumaravel A, Zelisko A, Schauer P, Lopez R, Kroh M, Stevens T. Acute pancreatitis in patients after bariatric surgery: incidence, outcomes, and risk factors. Obes Surg 2014; 24: 2025-30.
[9] Sugiyama M, Atomi Y. Risk factors for acute biliary pancreatitis. Gastrointest Endosc 2004; 60: 210-2.
[10] Dinarello CA. IL-18: A TH1-inducing, proinflammatory cytokine and new member of the IL-1 family. J Allergy Clin Immunol 1999; 103: 11-24.
[11] Friedberg EC. DNA damage and repair. Nature 2003; 421: 436-440.
[12] Kalina U, Ballas K, Koyama N, Kauschat D, Miething C, Arnemann J, Martin H, Hoelzer D, Ottmann OG. Genomic organization and regulation of the human interleukin-18 gene. Scand J Immunol 2000; 52: 525-30.
[13] Giedraitis V, He B, Huang WX, Hillert J. Cloning and mutation analysis of the human IL-18 promoter: a possible role of polymorphisms in expression regulation. J Neuroimmunol 2001; 112: 146-52.
[14] Jiang H, Cao H, Liu G, Huang Q, Li Y. IL-18 promoter -137G/C polymorphism correlates with chronic hepatitis B and affects the expression of interleukins. Acta Virol 2014; 58: 28-33.
[15] Lu Y, Bao JG, Deng Y, Rong CZ, Liu YQ, Huang XL, Song LY, Li S, Qin X. Role of IL-18 Gene Promoter Polymorphisms, Serum IL-18 Levels, and Risk of Hepatitis B Virus-related Liver Disease in the Guangxi Zhuang Population: a Retrospective Case-Control Study. Asian Pac J Cancer Prev 2015; 16: 6019-26.
[16] Cai F, Cui N, Ma H, Wang X, Qiao G, Liu D. Interleukin-10 -1082A/G polymorphism is associated with the development of acute pancreatitis in a Chinese population. Int J Clin Exp Pathol 2015; 8: 15170-6.
[17] Li D, Li J, Wang L, Zhang Q. Association between IL-1β, IL-8, and IL-10 polymorphisms and risk of acute pancreatitis. Genet Mol Res 2015; 14: 6635-41.
[18] Bao XB, Ma Z, Gu JB, Wang XQ, Li HG, Wang WY. IL-8 -251T/A polymorphism is associated with susceptibility to acute pancreatitis. Genet Mol Res 2015; 14: 1508-14.
[19] Chi DZ, Chen J, Huang DP. Influence of interleukin-1β and interleukin-6 gene polymorphisms on the development of acute pancreatitis. Genet Mol Res 2015; 14: 975-80.
[20] Marshall DJ, Rudnick KA, McCarthy SG, Mateo LR, Harris MC, McCauley C, Snyder LA. Interleukin-18 enhances Th1 immunity and tumor protection of a DNA vaccine. Vaccine 2006; 24: 244-53.
[21] Zeller T, Haase T, Müller C, Riess H, Lau D, Zeller S, Krause J, Baumert J, Pless O, Dupuis J, Wild PS, Eleftheriadis M, Waldenberger M, Zeilinger S, Ziegler A, Peters A, Tiret L, Proust C, Marzi C, Munzel T, Strauch K, Prokisch H, Lackner KJ, Herder C, Thorand B, Benjamin EJ, Blankenberg S, Koenig W, Schnabel RB. Molecular Characterization of the NLRC4 Expression in Relation to Interleukin-18 Levels. Circ Cardiovasc Genet 2015; 8: 717-26.
[22] Angelo HD, Gomes Silva II, Oliveira RD, Louzada-Júnior P, Donadi EA, Crovella S, Maia MM, de Souza PR, Sandrin-Garcia P. Interleukin-18, interleukin-12B and interferon-γ gene polymorphisms in Brazilian patients with rheumatoid arthritis: a pilot study. Tissue Antigens 2015; 86: 276-8.
[23] Chung JH, Lee YC, Eun YG, Chung JH, Kim SK, Chon S, Oh SJ, Rhee SY, Hong IK. Single Nucleotide Polymorphism of Interleukin-18 and Interleukin-18 Receptor and the Risk of Papillary Thyroid Cancer. Exp Clin Endocrinol Diabetes 2015; 123: 598-603.
[24] Zhou C, Ouyang N, Li QH, Luo SX, He Q, Lei H, Liu Q. The -137G/C single nucleotide polymorphism in IL-18 gene promoter contributes to tuberculosis susceptibility in Chinese Han population. Infect Genet Evol 2015; 36: 376-80.
[25] Gao SJ, Zhang L, Lu W, Wang L, Chen L, Zhu Z, Zhu HH. Interleukin-18 genetic polymorphisms contribute differentially to the susceptibility to Crohn's disease. World J Gastroenterol 2015; 21: 8711-22.
[26] Janiak A, Leśniowski B, Jasińska A, Pietruczuk M, Małecka-Panas E. Interleukin 18 as an early marker or prognostic factor in acute pancreatitis. Prz Gastroenterol 2015; 10: 203-7.
[27] Liang J, Zhou Y, Wang Z, Chen H. Relationship between liver damage and serum levels of IL-18, TNF-alpha and NO in patients with acute pancreatitis. Nan Fang Yi Ke Da Xue Xue Bao 2010; 30: 1912-4.
[28] Pastor CM, Morel DR, Vonlaufen A, Schiffer E, Lescuyer P, Frossard JL. Delayed production of IL-18 in lungs and pancreas of rats with acute pancreatitis. Pancreatology 2010; 10: 752-7.
[29] Meng H, Gong J, Fang L, Song Z, Wu F, Zhou B, Qian M. Effect of interferon-γ on NF-κB and cytokine IL-18 and IL-27 in acute pancreatitis. Bosn J Basic Med Sci 2013; 13: 114-8.