ORIGINAL ARTICLE

Korean J Intern Med 2018;33:1103-1110
https://doi.org/10.3904/kjim.2017.133

Association of a genetic polymorphism of *IL1RN* with risk of acute pancreatitis in a Korean ethnic group

Jin Woo Park[1,*], Ja Sung Choi[1,*], Ki Joon Han[1], Sang Heun Lee[1], Eui Joo Kim[2], and Jae Hee Cho[2]

[1]Division of Gastroenterology, Department of Internal Medicine, International St. Mary's Hospital, Catholic Kwandong University College of Medicine, Incheon; [2]Division of Gastroenterology, Department of Internal Medicine, Gachon University Gil Medical Center, Incheon, Korea

Received: March 14, 2017
Revised : May 12, 2017
Accepted: May 29, 2017

Correspondence to
Jae Hee Cho, M.D.
Division of Gastroenterology, Department of Internal Medicine, Gachon University Gil Medical Center, 21 Namdong-daero 774beon-gil, Namdong-gu, Incheon 21565, Korea
Tel: +82-32-460-3778
Fax: +82-32-460-3408
E-mail: jhcho9328@gmail.com

*These authors contributed equally to this work.

Background/Aims: Several epidemiological studies have validated the association of interleukin gene polymorphisms with acute pancreatitis (AP) in different populations. However, there have been few studies in Asian ethnic groups. We aimed to investigate the relationships between inflammatory cytokine polymorphisms and AP as pilot research in a Korean ethnic group.

Methods: Patients who had been diagnosed with AP were prospectively enrolled. DNA was extracted from whole blood, and DNA sequencing was subsequently performed. Single-nucleotide polymorphisms (SNPs) of the interleukin 1β (*IL1B*), interleukin 1 receptor antagonist (*IL1RN*), and tumor necrosis factor α (TNFA) genes of patients with AP were compared to those of normal controls.

Results: Between January 2011 and January 2013, a total of 65 subjects were enrolled (40 patients with AP vs. 25 healthy controls). One intronic SNP (IL1RN –1129T>C, rs4251961) was significantly associated with the risk of AP (odds ratio, 0.304; 95% confidence interval, 0.095 to 0.967; $p = 0.043$). However, in our study, AP was not found to be associated with polymorphisms in the promoter regions of inflammatory cytokine genes, including IL1B (–118C>T, c47+242C>T, +3954C/T, and –598T>C) and *TNFA* (–1211T>C, –1043C>A, –1037C>T, –488G>A, and –418G>A).

Conclusions: *IL1RN* –1129T>C (rs4251961) genotypes might be associated with a significant increase of AP risk in a Korean ethnic group.

Keywords: Pancreatitis; Polymorphism, single nucleotide; Interleukins; Tumor necrosis factor-alpha

INTRODUCTION

Acute pancreatitis (AP) is a common disease with an annual incidence of 13 to 45 per 100,000 population [1]. Mild AP requires only short-term hospitalization. However, 25% to 30% of patients experience severe attacks accompanied by organ failure and systemic complications. Severe AP is associated with a mortality rate of 10% to 15% despite intensive care [1-4]. Therefore, the early detection of patients at risk of severe AP is important for optimizing intensive care and improving patient outcomes. In this regard, many studies have reported methods for predicting the severity of AP, such as the Ranson score, the Acute Physiology and Chronic Health Examination II (APACHE II) score, the Bedside Index for Severity in Acute Pancreatitis (BISAP), and several individual biochemical markers, such as C-reactive protein and procalcitonin. In addition, imaging modalities such as endoscopic ultrasonography (EUS) and computed tomography can contribute to predicting AP severity

pISSN 1226-3303
eISSN 2005-6648
http://www.kjim.org

[5,6]. One recent study showed that EUS examination is the best predictor of the initial diagnosis and shortens the length of hospital stay in cases of AP. However, the clinical usefulness of EUS is limited in determining the etiology of AP [7].

Alcohol consumption and gallstones are two major risk factors for AP, and other factors such as genetics, drug use, and smoking probably also contribute to the risk of AP [1,4]. Because inflammation is an integral part of the pathological process of AP, inflammatory cytokines may act as risk factors for AP [2,4,8-10]. As inflammatory cytokines, interleukin (IL) and tumor necrosis factor (TNF) proteins could play key roles in the inflammatory response and immune system regulation. Therefore, these cytokines may also be associated with the onset and aggravation of AP. If we could identify the factors that determine the genetic susceptibility of an individual, it would help to identify patients at high risk for AP.

Several studies have shown an association between single-nucleotide polymorphisms (SNPs) of several genes (including interleukin 1β [*IL1B*], interleukin 1 receptor antagonist [*IL1RN*], and tumor necrosis factor α [*TNFA*]) and AP. Because SNPs differ in prevalence among ethnicities, the importance of SNPs associated with specific diseases also varies among populations, and the results of association studies conducted in one ethnic group may not hold true for other ethnicities. To date, there have been few studies in Asian populations.

We hypothesized that if patients could be identified as having a genetic predisposition for AP before developing severe AP, it would help prevent the aggravation of the disease. Therefore, we aimed to investigate the relationships between inflammatory cytokine polymorphisms and AP in a Korean ethnic group as pilot research.

METHODS

Subjects

From May 2011 to December 2012, we performed a prospective case-control study of DNA sequence analysis for patients who diagnosed with AP and got a medical checkup at Myongji Hospital in Goyang, Korea. Patients who had been diagnosed with AP were prospectively enrolled. DNA was extracted from whole blood, and DNA sequencing was subsequently performed. The study participants were divided into two groups: healthy controls (n = 25) and patients with AP (n = 40). Clinical data and SNP frequencies were compared between these two groups. Patients in the AP group were classified as having mild or severe AP depending on their accompanying local and systemic complications. Blood obtained from subjects was stored in ethylenediaminetetraacetic acid-containing tubes at –40°C and was subsequently sent to a laboratory facility for genotyping. Informed consent was obtained from all subjects. This study was approved by the Institutional Review Board (IRB No. 10-076) at Myongji Hospital and all patients gave written informed consent to participate in this study.

DNA sequencing

Polymerase chain reaction (PCR) was used to amplify 4 fragments of *IL1B*, 1 fragment of *IL1RN*, and 5 fragments of *TNFA*. The final volume of each reaction was 10 μL, consisting of 10 ng DNA, 0.5 μM of each primer pair, 0.25 mM deoxyribonucleoside triphosphates, 3 mM $MgCl_2$, 1 μL 1 × reaction buffer, and 0.25 units of Taq DNA polymerase (iNtRON Biotechnology, Seongnam, Korea). The PCR conditions were as follows: initial denaturation at 94°C for 5 minutes, followed by 35 cycles of denaturation at 94°C for 30 seconds, annealing at 60°C to 65°C for 30 seconds, initial extension at 72°C for 30 to 60 seconds, and final extension at 72°C for 10 minutes. The PCR products were purified using a MultiScreen 384-well PCR filter plate (Merck Millipore, Billerica, MA, USA). The purified products were then sequenced using a BigDye Terminator cycle sequencing kit (Applied Biosystems, Foster City, CA, USA) and an ABI 3730xl automated sequencer (Applied Biosystems). The sequencing primers were the same as those used for PCR amplification. Mutation analyses were performed using Polyphred 5.04 software (http://droog.gs.washington.edu/polyphred).

Genotype assay

A SNaPshot SNP genotyping assay was performed according to the manufacturer's instructions (SNaPshot Multiplex Kit, Applied Biosystems). Analysis was carried out using GeneMapper version 4.0 (Applied Biosystems).

Statistical analysis

Significant deviations of the genotype frequencies from the Hardy-Weinberg equilibrium were identified us-

https://doi.org/10.3904/kjim.2017.133

ing a permutation test for each SNP. We considered the genetic inheritance models of dominant, recessive, codominant, and additive for each SNP. Genotype and allele frequencies were compared between groups using the chi-square, Cochran-Armitage trend, Fisher exact, or Jonckheere-Terpstra test as appropriate. Multiple logistic regression analysis was employed to calculate odds ratios (ORs) and 95% confidence intervals (CIs) to assess the risk of phenotypes.

Data analysis was performed using SAS version 9.1.3 (SAS Inc., Cary, NC, USA). All tests were two tailed and p values < 0.05 were considered statistically significant.

RESULTS

Baseline characteristics

The mean ages of the AP and control groups were 66.22 ± 10.85 and 62.48 ± 9.01 years, respectively (p = 0.199), while the percentages of male patients were 55% and 48%, respectively (p = 0.310). Patients with AP were divided into those with mild AP (55%) and severe AP (45%). AP had local complications in 15 patients (37.5%). The main causes of AP among our cohort were alcohol (55%), gallstone (30%), and idiopathic (15%) (Table 1).

SNPs of *IL1B*, *IL1RN*, and *TNFA*

All SNPs of the three genes identified in this study are shown in Table 2. There were four SNPs in *IL1B* (–118C>T, c47+242C>T, +3954C/T, and –598T>C), 1 SNP in *IL1RN* (–1129T>C), and five SNPs in TNFA (–1211T>C, –1043C>A, –1037C>T, –488G>A, and –418G>A).

Associations between SNPs and AP

The results showed that the frequency of one intronic SNP significantly differed between the two groups, pro-

Table 1. Baseline characteristics of all subjects (n = 60)

Characteristic	Acute pancreatitis	Control	*p* value
No. of patients	40 (61.5)	25 (38.5)	-
Age, yr	66.22 ± 10.85	62.48 ± 9.01	0.199
Sex, male:female	22:18	12:13	0.310
Severity			
Mild	22 (55)	-	
Severe	18 (45)	-	
Complication			
Local complication	15 (37.5)	-	
No complication	25 (62.5)	-	
Etiology			
Alcohol	22 (55)	-	
Gallstone	12 (30)	-	
Idiopathic	6 (15)	-	

Values are presented as number (%) or mean ± standard deviation.

Table 2. SNPs of *IL1RN*, *IL1B*, and *TNFA*

	IL1B		*IL1RN*		*TNFA*	
	SNP ID	SNP name	SNP ID	SNP name	SNP ID	SNP name
1	rs1143634	–118C>T	rs4251961	–1129T>C	rs1799964	–1211T>C
2	rs1143629	c47+242C>T	-	-	rs1800630	–1043C>A
3	rs1143627	+3954C/T	-	-	rs1799724	–1037C>T
4	rs16944	–598T>C	-	-	rs1800629	–488G>A
5	-	-	-	-	rs361525	–418G>A

SNP, single-nucleotide polymorphism; *IL1RN*, interleukin 1 receptor antagonist; *IL1B*, interleukin 1β; *TNFA*, tumor necrosis factor α.

viding evidence for a significant association between *IL1RN* –1129T>C (rs4251961) and AP risk (OR, 0.304; 95% CI, 0.095 to 0.967; $p = 0.043$) (Table 3). For *IL1RN* –1129T>C, the TT major homogenotype was more frequent in the AP group than in the control group (87.5% vs. 68%, $p = 0.043$). These findings imply that the minor C allele of *IL1RN* –1129T>C (rs4251961) is associated with a significant increase of AP risk. However, there were no significant associations between SNPs and the severity or complications of AP (Tables 4 and 5).

DISCUSSION

Our study is the first to investigate SNPs of *IL1B*, *IL-1RN*, and *TNFA* in Korean AP subjects. In addition, we aimed to investigate whether specific genotypes are associated with AP. Among a total of 65 SNPs, one SNP in

Table 3. SNP genotypes in acute pancreatitis

SNP	SNP ID	MAF	AP (n = 40)	Control (n = 25)	*p* value	Functional consequence	OR (95% CI)
IL1RN –1129T>C	rs4251961	0.0625	-	-	0.043[a]	Intron	0.304 (0.095–0.967)
TT	-	-	35 (87.5)	17 (68)	-	-	-
CT	-	-	5 (12.5)	7 (28)	-	-	-
CC	-	-	0	1 (4)	-	-	-

Values are presented as number (%)
SNP, single nucleotide polymorphism; MAF, minor allele frequency; AP, acute pancreatitis; OR, odds ratio; CI, confidence interval.
[a]Chi-square test with dominant model.

Table 4. SNP genotypes and AP severity

SNP ID	MAP/C		SAP/C		MAP/SAP	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value
rs1143627	1.351 (0.49–3.725)	0.999	1.778 (0.613–5.157)	0.590	1.316 (0.447–3.877)	0.999
rs1143629	1.386 (0.497–3.867)	0.999	1.824 (0.611–5.444)	0.568	1.316 (0.439–3.944)	0.999
rs1143634	1.214 (0.428–3.449)	0.999	2.882 (0.146–56.765)	0.998	1.400 (0.467–4.201)	0.346
rs16944	1.351 (0.49–3.725)	0.999	1.778 (0.613–5.157)	0.590	1.316 (0.447–3.877)	0.999
rs4251961	0.333 (0.062–1.791)	0.320	0.268 (0.038–1.887)	0.270	0.804 (0.084–7.664)	0.999
rs1799964	0.993 (0.257–3.837)	0.999	1.500 (0.396–5.682)	0.998	1.510 (0.381–5.982)	0.999
rs1800630	0.829 (0.204–3.36)	0.999	1.050 (0.255–4.318)	0.998	1.267 (0.282–5.681)	0.999
rs1799724	0.788 (0.176–3.524)	0.999	0.361 (0.049–2.661)	0.628	0.459 (0.057–3.673)	0.999
rs1800629	2.009 (0.324–12.441)	0.999	2.527 (0.404–15.815)	0.650	1.258 (0.249–6.357)	0.999
rs361525	1.214 (0.428–3.449)	0.859	1.7 (0.576–5.018)	0.715	1.229 (0.04–37.903)	0.999

SNP, single nucleotide polymorphism; AP, acute pancreatitis; MAP, mild acute pancreatitis; C, control; SAP, severe acute pancreatitis; OR, odds ratio; CI, confidence interval.

https://doi.org/10.3904/kjim.2017.133

Table 5. SNP genotypes and AP severity

SNP ID	Local Cx/C		No Cx with AP/C		Local Cx/no Cx with AP	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value
rs1143627	1.556 (0.505–4.79)	0.999	1.514 (0.569–4.032)	0.935	1.027 (0.339–3.112)	0.999
rs1143629	1.58 (0.496–5.04)	0.999	1.553 (0.576–4.188)	0.867	1.017 (0.328–3.16)	0.999
rs1143634	3.500 (0.177–69.347)	0.871	1.302 (0.476–3.564)	0.952	1.248 (0.405–3.841)	0.198
rs16944	1.556 (0.505–4.79)	0.999	1.514 (0.569–4.032)	0.935	1.027 (0.339–3.112)	0.999
rs4251961	0.325 (0.046–2.313)	0.470	0.291 (0.054–1.554)	0.198	1.119 (0.117–10.712)	0.999
rs1799964	1.909 (0.494–7.384)	0.753	0.855 (0.223–3.275)	0.999	2.234 (0.557–8.958)	0.487
rs1800630	1.313 (0.314–5.488)	0.999	0.716 (0.178–2.881)	0.999	1.833 (0.405–8.297)	0.999
rs1799724	0.212 (0.015–2.919)	0.378	0.838 (0.201–3.491)	0.999	0.253 (0.018–3.574)	0.560
rs1800629	2.410 (0.353–16.437)	0.729	2.136 (0.365–12.489)	0.890	1.128 (0.216–5.903)	0.999
rs361525	1.714 (0.053–55.646)	0.590	1.128 (0.109–11.716)	0.951	1.69 (0.055–52.262)	0.999

SNP, single nucleotide polymorphism; AP, acute pancreatitis; Cx, complication; C, control; OR, odds ratio; CI, confidence interval.

IL1RN was significantly associated with AP. The C allele of *IL1RN* –1129T>C was significantly associated with AP, though this was not significant after adjustment for age and sex.

AP is characterized as inflammation of pancreas associated with a systemic inflammatory response syndrome or multi-organ dysfunction syndrome [2,11,12]. The inflammatory process is originated by intrapancreatic protease activation and AP progresses through three stages: local inflammation of the pancreas, a systemic inflammatory response that can result in single or multiple organ failure, and finally infection by translocation of bacteria from the gut [13]. If the response to the initial injury is inappropriate, the systemic inflammatory response syndrome will supervene. Systemic symptoms are due to the action of inflammatory cytokines, which are responsible for most of the morbidity and mortality of pancreatitis. The clinical course of acute inflammatory diseases such as AP has been suggested to have a genetic basis, because specific cytokine gene polymorphisms can cause differences in the inflammatory process [13,14].

The *IL1* gene cluster contains three related genes within a 430-kb region of DNA on the long arm of human chromosome 2, namely *IL1A*, *IL1B*, and *IL1RN*. IL1A and *IL1B* are strong inducers of inflammation, while *IL1RN* encodes IL-1 receptor antagonist (IL-1RA), which is an endogenous anti-inflammatory cytokine that binds to the IL-1 receptor without activating the target cell. Infectious and inflammatory diseases are typically associated with a strong elevation in the serum levels of IL-1RA to about 100-fold higher than those of IL-1β [15-17]. Many studies have focused on investigating the potential association between IL gene polymorphisms and AP risk. The biological role of IL-1β is to enhance the inflammatory response through inducing the expression of other proinflammatory cytokine genes including *TNFA*, *IL2*, and *IL6*. A recent systematic review did not show a significant association between *IL1B* +3954C/T (rs1143634) or –511C/T (rs16944) with AP [4]. Previous studies found that there was no significant association between *IL1B* +3954C/T and AP risk in British populations [10,15]. These findings are similar to those of our study, in which polymorphisms in the *IL1B* promoter region, such as *IL1B* –118C>T (rs1143627), c.47+242C>T (rs1143629), +395C/T (rs1143634), and –598T>C (rs16944)

were not associated with the risk of AP. In recent studies involving Korean subjects, associations have been reported between aspirin-induced peptic ulcer and SNPs, including three exonic SNPs (*IL1B* –581C/T [rs1143627], *IL1B* –1061C/T [rs16944], and *IL1RN* –1129 [rs4251961]) and one intronic SNP (*IL1B* IVS2+242C/T) [18].

IL1RN encodes IL-1RA, which has an anti-inflammatory effect via competitive inhibition of ligand binding to the IL-1 receptor. Before or after the induction of AP, IL1RA inhibits the rise in the levels of pro-inflammatory cytokines and is associated with a decreased severity of pancreatitis and a reduction in pancreatic damage. Therefore, an imbalance between IL-1 and IL-1ra protein levels have also been associated with the general inflammation process such as systemic inflammatoty response syndrome or sepsis. The presence of *IL1RN* polymorphism will also play an important role in the susceptibility of AP patients to septic shock. *IL1RN* is functionally important and is linked to other genes [13,18-20]. *IL1RN* contains a variable number of tandem repeat units constructed from two to six copies of an 86-base-pair sequence. In the second intron of *IL1RN* gene, the most common allele is allele 1 (frequency 0.74), which contains 4 repeats. Allele 2 (frequency 0.21) contains 2 repeats. The frequency of allele 2 is increased in several autoimmune or inflammatory diseases [15,21-24]. One study reported that the minor alleles of *IL1RN* 1018 (rs4251961), and 13888 (rs2232354) are associated with lower IL-1RA production and thus higher levels of inflammatory biomarkers [25]. The study of Carrol et al. [20] showed that the minor C allele of an *IL1RN* (C/T) promoter polymorphism (rs4251961) correlated with the concentration of IL-1RA in human infection. When these findings are compared with our result, we can derive the relevance of the minor C allele of rs4251961 and AP. Furthermore, a few studies have shown an association between SNPs in *IL1RN* and AP. The study of Smithies et al. [13] reported a significant association between an SNP of *IL1RN* and the severity of AP in a British population. Although our study did not identify an association between SNPs of *IL1RN* and the severity of AP, the C allele of *IL1RN* –1129T>C (rs4251961) was found to be associated with AP risk.

TNF-α is an important mediator of the inflammatory response and is central to the initiation of the cytokine network, which leads to the production of other proinflammatory cytokines such as IL-6 and IL-8 [26,27]. Several studies have focused on the association between *TNFA* and AP [3,28,29]. The study of Yin et al. [27] found that there was no significant association between *TNFA* –308A/G and AP risk. Similarly, in our study, no associations were identified between AP and *TNFA* polymorphisms, including *TNFA* –1211T>C (rs1799964), –1043C>A (rs1800630), –1037C>T (rs1799724), –488G>A (rs1800629), and –418G>A (rs361525). However, in contrast, it has also been reported that the *TNFA* –308 A allele was associated with the risk of AP and the development of septic shock in severe AP [12].

Our study has several limitations. First, our sample size was too small and thus may not be representative of general genetic trends in the Korean population. To investigate the associations between SNPs and AP, we performed a full DNA sequence analysis of the target genes and proposed several candidate SNPs related to AP. Second, the functional effect of these SNPs is still unknown. There is a possibility that they may affect the promoter activity by influencing the binding affinity of nuclear proteins, but no pathogenic effect has yet been established for these SNPs. Third, our study examined the relationships between *IL1B* polymorphisms and the severity of AP, but no significant results were found. The study of Zhang et al. [30] reported that the *IL1B* –1082G allele played an important role in the susceptibility of patients with severe AP to septic shock. In a Chinese study, the *IL1B* +3954C/T and –511C/T polymorphisms were associated with AP risk [4]. However, these results require further validation. Future studies with large sample sizes will be required for the further evaluation of genetic associations with AP risk and severity. Moreover, this study is limited to the Korean population and is not representative of the world's population. Recently, the Atlanta classification was divided into mild, moderately severe, and severe pancreatitis, but we had already adopted a classification scheme of mild and severe AP at the beginning of this study. Therefore, further investigations of AP including functional assays for these SNPs are warranted. Despite these noted limitations, this study is significant as the first genetic association study for AP in a Korean ethnic group.

In conclusion, Korean adults with *IL1RN* –1129T>C (rs4251961) had an increased risk of AP. This SNP may become a candidate biomarker for identifying patients

https://doi.org/10.3904/kjim.2017.133

at high risk for AP, although further investigation and validation are needed.

KEY MESSAGE

1. This is the first study to present the relationships between inflammatory cytokine polymorphisms and acute pancreatitis (AP) in a Korean ethnic group.
2. *IL1RN* –1129T>C is associated with a significant increase of AP risk

Conflict of interest

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Lankisch PG, Apte M, Banks PA. Acute pancreatitis. Lancet 2015;386:85-96.
2. Johnson CD, Besselink MG, Carter R. Acute pancreatitis. BMJ 2014;349:g4859.
3. Tukiainen E, Kylanpaa ML, Puolakkainen P, et al. Polymorphisms of the TNF, CD14, and HSPA1B genes in patients with acute alcohol-induced pancreatitis. Pancreas 2008;37:56-61.
4. Yin YW, Sun QQ, Feng JQ, Hu AM, Liu HL, Wang Q. Influence of interleukin gene polymorphisms on development of acute pancreatitis: a systematic review and meta-analysis. Mol Biol Rep 2013;40:5931-5941.
5. Lee KJ, Kim HM, Choi JS, Kim YJ, Kim YS, Cho JH. Comparison of predictive systems in severe acute pancreatitis according to the revised Atlanta Classification. Pancreas 2016;45:46-50.
6. Cho JH, Choi JS, Hwang ET, et al. Usefulness of scheduled follow-up CT in discharged patients with acute pancreatitis. Pancreatology 2015;15:642-646.
7. Cho JH, Jeon TJ, Choi JS, et al. EUS finding of geographic hyperechoic area is an early predictor for severe acute pancreatitis. Pancreatology 2012;12:495-501.
8. de-Madaria E, Martinez J, Sempere L, et al. Cytokine genotypes in acute pancreatitis: association with etiology, severity, and cytokine levels in blood. Pancreas 2008;37:295-301.
9. Mayer J, Rau B, Gansauge F, Beger HG. Inflammatory mediators in human acute pancreatitis: clinical and pathophysiological implications. Gut 2000;47:546-552.
10. Norman J. The role of cytokines in the pathogenesis of acute pancreatitis. Am J Surg 1998;175:76-83.
11. Banks PA. Epidemiology, natural history, and predictors of disease outcome in acute and chronic pancreatitis. Gastrointest Endosc 2002;56(6 Suppl):S226-S230.
12. Bishehsari F, Sharma A, Stello K, et al. TNF-alpha gene (TNFA) variants increase risk for multi-organ dysfunction syndrome (MODS) in acute pancreatitis. Pancreatology 2012;12:113-118.
13. Smithies AM, Sargen K, Demaine AG, Kingsnorth AN. Investigation of the interleukin 1 gene cluster and its association with acute pancreatitis. Pancreas 2000;20:234-240.
14. Stuber F, Petersen M, Bokelmann F, Schade U. A genomic polymorphism within the tumor necrosis factor locus influences plasma tumor necrosis factor-alpha concentrations and outcome of patients with severe sepsis. Crit Care Med 1996;24:381-384.
15. Santtila S, Savinainen K, Hurme M. Presence of the IL-1RA allele 2 (IL1RN*2) is associated with enhanced IL-1beta production in vitro. Scand J Immunol 1998;47:195-198.
16. Hu Z, Shao M, Chen Y, et al. Allele 2 of the interleukin-1 receptor antagonist gene (IL1RN*2) is associated with a decreased risk of primary lung cancer. Cancer Lett 2006;236:269-275.
17. Xue H, Lin B, Ni P, Xu H, Huang G. Interleukin-1B and interleukin-1 RN polymorphisms and gastric carcinoma risk: a meta-analysis. J Gastroenterol Hepatol 2010;25:1604-1617.
18. Cho JH, Choi JS, Chun SW, Lee S, Han KJ, Kim HM. The IL-1B genetic polymorphism is associated with aspirin-induced peptic ulcers in a Korean ethnic group. Gut Liver 2016;10:362-368.
19. El-Omar EM, Carrington M, Chow WH, et al. Interleukin-1 polymorphisms associated with increased risk of gastric cancer. Nature 2000;404:398-402.
20. Carrol ED, Payton A, Payne D, et al. The IL1RN promoter rs4251961 correlates with IL-1 receptor antagonist concentrations in human infection and is differentially regulated by GATA-1. J Immunol 2011;186:2329-2335.
21. Tarlow JK, Blakemore AI, Lennard A, et al. Polymorphism in human IL-1 receptor antagonist gene intron 2 is caused by variable numbers of an 86-bp tandem repeat. Hum Genet 1993;91:403-404.

22. Mansfield JC, Holden H, Tarlow JK, et al. Novel genetic association between ulcerative colitis and the anti-inflammatory cytokine interleukin-1 receptor antagonist. Gastroenterology 1994;106:637-642.
23. Tarlow JK, Clay FE, Cork MJ, et al. Severity of alopecia areata is associated with a polymorphism in the interleukin-1 receptor antagonist gene. J Invest Dermatol 1994;103:387-390.
24. Blakemore AI, Cox A, Gonzalez AM, et al. Interleukin-1 receptor antagonist allele (IL1RN*2) associated with nephropathy in diabetes mellitus. Hum Genet 1996;97:369-374.
25. Reiner AP, Wurfel MM, Lange LA, et al. Polymorphisms of the IL1-receptor antagonist gene (IL1RN) are associated with multiple markers of systemic inflammation. Arterioscler Thromb Vasc Biol 2008;28:1407-1412.
26. Formela LJ, Galloway SW, Kingsnorth AN. Inflammatory mediators in acute pancreatitis. Br J Surg 1995;82:6-13.
27. Yin YW, Hu AM, Sun QQ, et al. Association between tumor necrosis factor-alpha gene -308A/G polymorphism and the risk of acute pancreatitis: a meta-analysis. J Surg Res 2012;178:409-414.
28. 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;129:633-640.
29. Schneider A, Pogue-Geile K, Barmada MM, Myers-Fong E, Thompson BS, Whitcomb DC. Hereditary, familial, and idiopathic chronic pancreatitis are not associated with polymorphisms in the tumor necrosis factor alpha (TNF-alpha) promoter region or the TNF receptor 1 (TNFR1) gene. Genet Med 2003;5:120-125.
30. Zhang DL, Zheng HM, Yu BJ, Jiang ZW, Li JS. Association of polymorphisms of IL and CD14 genes with acute severe pancreatitis and septic shock. World J Gastroenterol 2005;11:4409-4413.

https://doi.org/10.3904/kjim.2017.133