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.
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 MgCl₂, 1 μL 1 x 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-
Park JW, et al. Association of a genetic polymorphism of \textit{IL1RN} with risk of acute pancreatitis

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 \textit{IL1B}, \textit{IL1RN}, and \textit{TNFA}
All SNPs of the three genes identified in this study are shown in Table 2. There were four SNPs in \textit{IL1B} (−118C>T, c47+242C>T, +3954C>T, and −598T>C), 1 SNP in \textit{IL1RN} (−1129T>C), and five SNPs in \textit{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 (36) | - |
| Idiopathic | 6 (15) | - |

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

Table 2. SNPs of \textit{IL1RN}, \textit{IL1B}, and \textit{TNFA}

| \textit{IL1B} | \textit{IL1RN} | \textit{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 | - | - | - | - | rs365125 | −418G>A |

SNP, single-nucleotide polymorphism; \textit{IL1RN}, interleukin 1 receptor antagonist; \textit{IL1B}, interleukin 1β; \textit{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, IL1RN, 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

| 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 | 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.

| SNP ID | MAP/C | \( p \) value | SAP/C | \( p \) value | MAP/SAP | \( p \) value |
|--------|-------|-------------|-------|-------------|---------|-------------|
| rs1143627 | 1.351 | (0.49–3.725) | 0.999 | 0.320 | 0.268 | (0.062–1.791) | 0.062 | 0.999 |
| rs1143629 | 1.386 | (0.497–3.867) | 0.999 | 0.282 | 0.178 | (0.428–1.449) | 0.082 | 0.999 |
| rs1143634 | 1.214 | (0.497–3.867) | 0.999 | 0.146 | 0.361 | (0.49–3.725) | 0.062 | 0.999 |
| rs16944 | 1.351 | (0.49–3.725) | 0.999 | 0.703 | 0.590 | (0.428–1.449) | 0.062 | 0.999 |
| rs4251961 | 0.333 | (0.062–1.791) | 0.999 | 0.098 | 0.270 | (0.062–1.791) | 0.062 | 0.999 |
| rs1799964 | 0.993 | (0.257–3.837) | 0.999 | 0.361 | 0.150 | (0.257–3.837) | 0.257 | 0.999 |
| rs1800630 | 0.829 | (0.204–3.36) | 0.999 | 0.355 | 1.050 | (0.204–3.36) | 0.257 | 0.999 |
| rs1799724 | 0.788 | (0.176–3.524) | 0.999 | 0.404 | 0.361 | (0.176–3.524) | 0.257 | 0.999 |
| rs1800629 | 2.009 | (0.324–12.441) | 0.999 | 0.404 | 0.576 | (0.324–12.441) | 0.257 | 0.999 |
| rs361525 | 1.214 | (0.428–3.449) | 0.999 | 0.576 | 0.715 | (0.428–3.449) | 0.257 | 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.
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 (rs1143620), +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 −1082G [rs1210944], 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 inflammatory 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 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 inflammatory 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 pro-inflammatory cytokines [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 (rs1800629), −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.
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. \textit{IL1RN} $\text{−1129T>C}$ is associated with a significant increase of AP risk.

Conflict of interest

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

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