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ORIGINAL ARTICLE

The first association study of single-nucleotide polymorphisms (SNPs) of the *IFITM1* gene with influenza H1N1 2009 pandemic virus infection

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Abstract

Background The interferon-induced transmembrane (IFITM) protein family consists of interferon-stimulated genes (ISGs) that show potent antiviral capacity against a broad range of viruses. Many studies have been performed to investigate an association between *IFITM3* polymorphisms and pandemic influenza A 2009 H1N1 virus infection. However, an association study of *IFITM1* polymorphisms with susceptibility to this infection has not been reported thus far.

Objective To identify an association between the susceptibility to pandemic influenza A 2009 H1N1 virus infection and *IFITM1* polymorphisms, we compared genotype, allele and haplotype frequencies of the *IFITM1* gene between healthy controls and pandemic influenza A 2009 H1N1-infected patients. In addition, we investigated linkage disequilibrium (LD) by Haploview 4.2 and the binding ability of transcription factors according to *IFITM1* polymorphism alleles by PROMO. Furthermore, we measured the LD value between the *IFITM1* gene and the *IFITM3* gene.

Results We found 3 novel single-nucleotide polymorphisms (SNPs) and did not find an association between *IFITM1* SNPs and susceptibility to pandemic influenza A 2009 H1N1 virus infection. We found strong LD among *IFITM1* SNPs but did not find a difference in the transcription factor-binding ability according to regulatory *IFITM1* SNP alleles. In addition, we found strong LD between *IFITM1* SNPs and *IFITM3* SNPs.

Conclusion To the best of our knowledge, this report is the first association study of the susceptibility to pandemic influenza A 2009 H1N1 virus infection and *IFITM1* polymorphisms.

Keywords IFITM1 · IFITM3 · Influenza A virus · H1N1 · Single nucleotide polymorphism

Introduction

In response to viral invasion, viral sensor proteins of the host immune system, including melanoma differentiation-associated gene-5 (MDA-5), retinoic acid-inducible gene 1 (RIG-1) and Toll-like receptors (TLRs), recognize viral antigens and activate interferon secretion (Uematsu and Akira 2007; Sarkar et al. 2008; Reikine et al. 2014; Brisse and Ly 2019). Secreted interferon binds to interferon receptor (IFNR) and stimulates the expression of interferon-stimulated genes (ISGs) mediated by the Janus kinase/signal transducers and activators of transcription (JAK/STAT) signaling pathway (Horvath 2004a, b; Schindler et al. 2007). Among various ISGs, previous studies have reported that the clustering of the interferon-induced transmembrane protein (IFITM) protein family showed potent antiviral capacity through blocking the internalization of a broad spectrum of viruses, including Ebola virus (EBOV), Marburg virus (MARV), severe acute respiratory syndrome coronavirus (SARS-CoV), dengue virus (DEV), West Nile virus (WNV), Zika virus (ZIKV) and influenza A virus (IAV) (Feeley et al. 2011; Bailey et al. 2012; Everitt et al. 2012; Diamond and Farzan 2013; Perreira et al. 2013; Bailey et al. 2014; Kim and Jeong 2017; Zani and Yount 2018; Bedford et al. 2019;

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Kim et al. 2019; Spence et al. 2019; Kim et al. 2020; Kim and Jeong 2020; Kim and Jeong 2021; Lee et al. 2019).

In a recent study, genetic polymorphisms of the *IFITM3* gene, a member of the IFITM protein family, were associated with the severity and/or susceptibility to pandemic influenza A 2009 H1N1 virus infection. The rs12252 single-nucleotide polymorphism (SNP), which is located in the splicing receptor site of the *IFITM3* gene and induces the production of an N-terminal-truncated form of IFITM3 protein, is associated with the severity of pandemic influenza A 2009 H1N1 infection (Everitt et al. 2012; Zhang et al. 2013; Mills et al. 2014; Xuan et al. 2015; Gaio et al. 2016; Pan et al. 2017). In addition, the rs34481144 and rs6598045 SNPs, which are located in the transcriptional regulatory region of the *IFITM3* gene, are also strongly related to the severity of and susceptibility to pandemic influenza A 2009 H1N1 virus infection, respectively (Allen et al. 2017; David et al. 2018; Kim et al. 2020). The IFITM1 protein, a member of the IFITM protein family, plays a pivotal role in the antiviral response of the host innate immune system. Unlike the IFITM3 protein, which is mainly expressed in the late endosome and prevents viral fusion, the IFITM1 protein mainly expressed in the cytosolic leaflet and blocks entry of viruses to the early endosome (Perreira et al. 2013). However, there are no association studies of genetic polymorphisms of the *IFITM1* gene with the susceptibility to pandemic influenza A 2009 H1N1 virus infection.

To identify an association between the susceptibility to pandemic influenza A 2009 H1N1 virus infection and *IFITM1* polymorphisms, we investigated the genotype, allele and haplotype frequencies of the *IFITM1* gene. In addition, we compared the genotype, allele and haplotype frequencies of the *IFITM1* gene between healthy controls and pandemic influenza A 2009 H1N1-infected patients and estimated an association between the susceptibility to pandemic influenza A 2009 H1N1 virus infection and the *IFITM1* polymorphisms. Furthermore, we investigated linkage disequilibrium (LD) by Haploview 4.2 and the binding ability of transcription factors according to *IFITM1* polymorphism alleles by PROMO. Last, we measured the LD value between the *IFITM1* and *IFITM3* genes.

Materials and methods

Ethics statements

Detailed information on all participants was described in a previous study (Kim et al. 2020). All samples were provided with informed consent under institutional review board-approved protocols. All procedures performed in the present study were approved according to guidelines of the institutional review board (IRB) of Jeonbuk National University and in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards (approval number: JBNU 2017-08-009). All the samples and related data were anonymized prior to study.

Genomic material

Genomic DNA was extracted from 200 µl of whole blood using a Blood Genomic DNA Isolation Kit (Qiagen, Valencia, California, USA) following the manufacturer's recommendations.

Amplification of the *IFITM1* gene and genetic analysis

The human *IFITM1* gene was amplified from genomic DNA using sense and antisense gene-specific primers. The sequences of the primers were as follows: IFITM1-F (AGT GAGGTGAGGGCTTTTGG) and IFITM1-R (CACAGT CACAGGGACACACA). Polymerase chain reaction (PCR) was carried out using GoTaq® DNA Polymerase (Promega, Fitchburg, Wisconsin, USA). The PCR mixture contained 20 pmol of each primer, 5 µl of 10 × *Taq* DNA polymerase buffer, 1 µl of 10 mM dNTP mixture and 2.5 units of *Taq* DNA polymerase. The PCR conditions for the IFITM1-F and IFITM1-R primers were 94 °C for 2 min to denature; 35 cycles of 94 °C for 45 s, 71 °C for 45 s, and 72 °C for 1 min 30 s; and then 1 cycle of 72 °C for 10 min to extend the reaction. PCR was performed using an S-1000 Thermal Cycler (Bio-Rad, Hercules, California, USA). The PCR products were eluted by a PCR Purification Kit (Thermo Fisher Scientific, Bridgewater, New Jersey, USA) and directly sequenced with an ABI 3730 automatic sequencer (ABI, Foster City, California, USA). Sequencing results were read by Finch TV software (Geospiza Inc, Seattle, USA), and genotyping was performed.

Statistical analysis

Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., USA). The differences in the distribution of genotypes, alleles and haplotypes of the *IFITM1* gene between cases and control populations were analyzed using the χ^2 test. The Hardy–Weinberg equilibrium (HWE) test and haplotype analysis were performed using Haploview 4.2 (Broad Institute, Cambridge, MA, USA). LD analysis was performed using coefficient r^2 values by the program Haploview version 4.2 (Broad Institute, Cambridge, MA, USA).

Prediction of transcription factors of the *IFITM1* gene

Binding sites and transcription factors were predicted by PROMO (http://alggen.lsi.upc.es/cgi-bin/promo_v3/promo

/promoinit.cgi?dirDB=TF_8.3). The maximum matrix dissimilarity rate was entered as a "0" value. Four major haplotypes of proximal promoter sequences of the *IFITM1* gene were identified and analyzed in this study.

Results

Investigation of polymorphisms of the *IFITM1* gene

To investigate the genotype and allele frequencies of *IFITM1* gene polymorphisms in the Korean population, we performed direct sequencing in 175 healthy controls and 30 H1N1 pandemic influenza 2009 virus-affected patients. Detailed information on the participants is described in Table 1. The sequenced products were homologous to the *IFITM1* gene of *Homo sapiens* registered in GenBank (Gene ID: 8519). We found a total of 3 novel SNPs, c.-416C > G, c.-327A > C and c.186 + 18G > A (Fig. 1). The c.-327A > C and c.186 + 18G > A SNPs were found in only healthy controls (Table 2).

Table 1 Detailed information on the study population

Characteristics	Cases	Controls
Number	30	175
Age	55.27 ± 17.88	62.43 ± 8.96
Sex (*n*, %)		
Male	11 (36.67)	61 (34.86)
Female	19 (63.33)	114 (65.14)
No. of *ICU admissions	1	**NA

**ICU* intensive care unit

***NA* not applicable

Evaluation of an association between *IFITM1* polymorphisms and susceptibility to H1N1 influenza 2009 pandemic virus infection in the Korean population

To examine an association between the genetic distribution of the *IFITM1* gene and susceptibility to H1N1 pandemic influenza 2009 virus infection, we compared the genotype, allele and haplotype frequencies of the *IFITM1* gene polymorphisms between the healthy controls and H1N1 pandemic influenza 2009 virus-affected patients. Interestingly, genotype and allele frequencies of all 3 SNPs of the *IFITM1* gene showed no association between healthy controls and H1N1 pandemic influenza 2009-affected patients (Table 2). Detailed information on the genotype and allele frequencies of SNPs of the *IFITM1* gene is described in Table 2. To analyze the haplotype frequencies, we investigated the distribution of haplotypes using Haploview 4.2. Three major haplotypes were found in the SNPs of the human *IFITM1* gene. The detailed degree of haplotype distribution is described in Table 3. In brief, a statistical comparison of 3 major haplotypes showed no significant distribution ($P > 0.9$) between healthy controls and H1N1 pandemic influenza

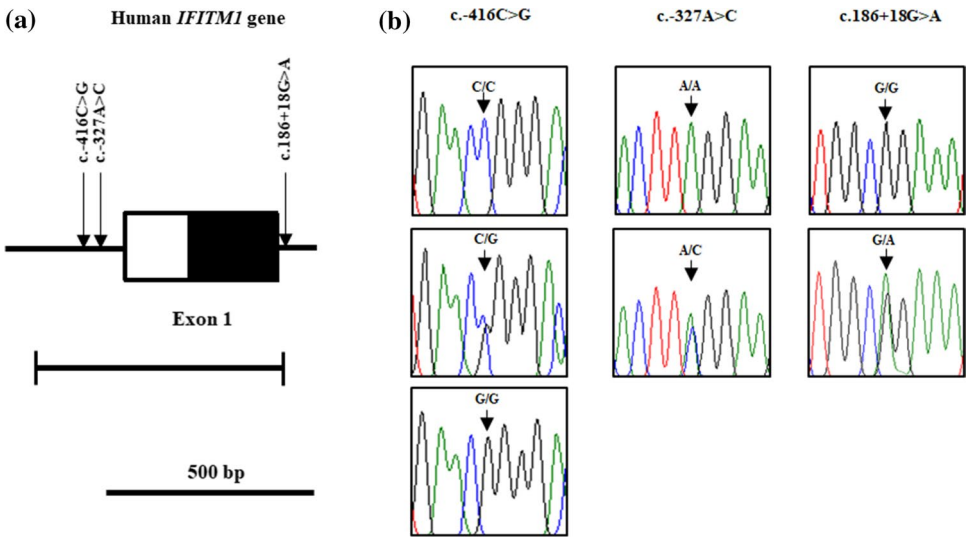

Fig. 1 Gene map and polymorphisms identified in the human interferon-induced transmembrane protein 1 (*IFITM1*) gene on chromosome 11. **a** The black block indicates the open reading frame (ORF), and the white block indicates the 5′ untranslated region (UTR). Horizontal bar with edges indicates the region sequenced. Arrows indicate the novel polymorphisms found in this study. **b** Electropherogram of 3 novel single-nucleotide polymorphisms (SNPs), c.-416C > G, c.-327A > C and c.186 + 18G > A, identified in this study. The four colors indicate individual bases of DNA sequence determined using an ABI 3730 automatic sequencer (blue: cytosine, red: thymine, black: guanine, green: adenine)

Table 2 Comparison of genotype and allele frequencies of the *IFITM1* polymorphisms between healthy controls and H1N1 pandemic influenza 2009 virus-affected patients in the Korean population

Polymorphisms	Total, *n*	Genotype frequencies, *n* (%)			*P* value	Allele frequencies, *n* (%)		*P* value	HWE
c.-416C > G		CC	CG	GG		C	G		
Control	175	101 (57.7)	61 (34.9)	13 (7.4)		263 (75.2)	87 (24.8)		0.376
Case	30	16 (53.3)	13 (43.3)	1 (3.4)	0.5980	45 (75)	15 (25)	0.9811	0.394
c.-327A > C		AA	AC	CC		A	C		
Control	175	174 (99.4)	1 (0.6)	0 (0)		349 (99.7)	1 (0.3)		0.969
Case	30	30 (100)	0 (0)	0 (0)	1.0	60 (100)	0 (0)	1.0	–
c.186 + 18G > A		GG	GA	AA		G	A		
Control	175	174 (99.4)	1 (0.6)	0 (0)		349 (99.7)	1 (0.3)		0.969
Case	30	30 (100)	0 (0)	0 (0)	1.0	60 (100)	0 (0)	1.0	–

Table 3 Comparison of haplotype frequencies of *IFITM1* polymorphisms between healthy controls and H1N1 pandemic influenza 2009 virus-affected patients in the Korean population

Haplotypes	Frequency		*P* value
	Control (350)	Case (60)	
CAG	263 (0.751)	45 (0.75)	0.9811
GAG	85 (0.243)	15 (0.25)	0.9052
Others	2 (0.006)	0 (0)	1.0

Table 4 Linkage disequilibrium (LD) among 3 polymorphisms of human *IFITM1* gene in the Korean populations

r^2	c.-416C > G	c.-327A > C	c.186 + 18G > A
c.-416C > G	–	–	–
c.-327A > C	0.009	–	–
c.186 + 18G > A	0.009	0	–

2009 virus-affected patients. We also investigated the LD among the three *IFITM1* SNPs with r^2 values. Notably, all the *IFITM1* SNPs showed weak LD ($r^2 < 0.3$, Table 4).

Transcription factor-binding ability according to alleles of SNPs in the promoter region of the *IFITM1* gene

We analyzed the binding capacity of transcription factors according to alleles of regulatory SNPs using PROMO. The proximal promoter located approximately 300 base pairs upstream of the transcription start site was classified into 4 major haplotypes, and the binding ability of transcription factors was predicted according to these haplotypes. Interestingly, there was no difference in the binding ability of transcription factors according to the 4 haplotypes of promoter sequences (Fig. 2).

Analysis of the genetic linkage between the *IFITM1* and *IFITM3* SNPs

To examine whether the *IFITM1* SNPs have genetic linkage with *IFITM3* SNPs, LD analysis was carried out among SNPs of these two genes in heathy controls and H1N1 pandemic influenza 2009 virus-affected patients. Detailed values are described in Tables 5, 6. In healthy controls (Table 5), the *IFITM1* c.-416C > G SNP showed strong LD with 5 *IFITM3* SNPs, c.-204G > T (0.422), c.-181T > C (0.851), c.-178A > C (0.866), c.-175T > C (0.866) and c.42C > T (0.321). The remaining *IFITM1* SNPs showed weak LD with *IFITM3* SNPs ($r^2 < 0.3$). In H1N1 pandemic influenza 2009 virus-affected patients (Table 6), the *IFITM1* c.-416C > G SNP showed strong LD with 4 *IFITM3* SNPs, c.-204G > T (0.536), c.-181T > C (0.5), c.-178A > C (0.5) and c.-175T > C (0.5).

Discussion

The IFITM1 protein is a member of the IFITM protein family, which is composed of IFITM 1, 2, 3, 5 and 10. IFITM family proteins are highly homologous with each other and contain a well-conserved CD225 domain, which consists of two major structures, transmembrane 1 and a conserved intracellular loop. The IFITM family in vertebrates can be divided into three subfamilies. IFITM1, 2 and 3 are crucial antiviral effectors, so these proteins can be classified into the immunity-related IFITM (IR-IFITM) subfamily. The *IFITM1* gene is located 4.8 kb downstream of the *IFITM3* gene, and the regulatory region of the *IFITM3* gene affects translational regulation of the *IFITM1* gene (Diamond and Farzan 2013; Smith et al. 2014; Zhao et al. 2018; Yanez et al. 2020). Since there apparently is a structural and functional relationship between *IFITM1* and *IFITM3* genes and the *IFITM3* gene showed a strong association with the severity of and susceptibility to pandemic influenza A 2009 H1N1

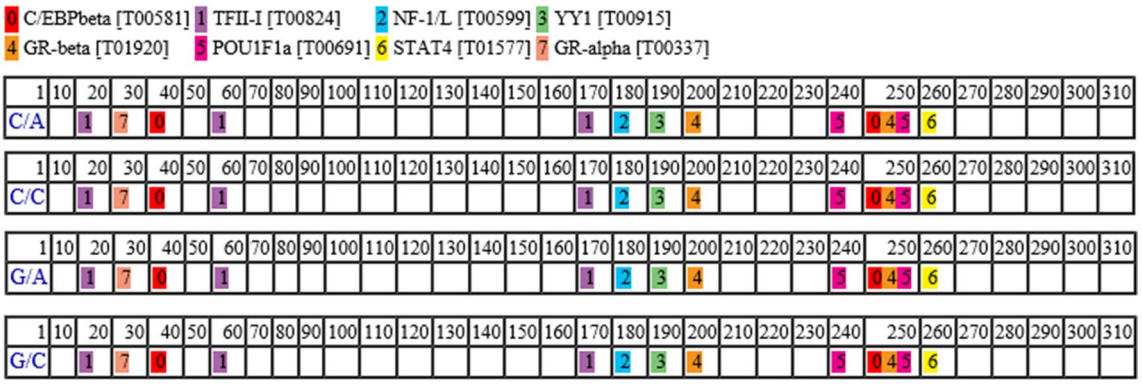

Fig. 2 Analysis of the binding ability of transcription factors among 4 haplotypes of proximal promoter sequences in the human *IFITM1* gene. C/A consists of the C allele of c.-416C > G and the A allele of c.-327A > C. C/C consists of the C allele of c.-416C > G and the C allele of c.-327A > C. G/A consists of the G allele of c.-416C > G and the A allele of c.-327A > C. G/C consists of the G allele of c.-416C > G and the C allele of c.-327A > C

virus infection, we investigated an association of the *IFITM1* gene with the susceptibility to pandemic influenza A 2009 H1N1 virus infection.

Since *IFITM1* polymorphisms have not been investigated thus far, we first investigated the polymorphisms of the *IFITM1* gene in the present study. We found a total of 3 novel SNPs, c.-416C > G, c.-327A > C and c.186 + 18G > A (Fig. 1, Table 2). In a previous study, we found 15 polymorphisms of the *IFITM3* gene in Korean populations. However, in the present study, we found only 3 SNPs in the same test groups (Kim et al. 2020). Of these 3 *IFITM1* SNPs, 2 SNPs are extremely rare SNPs, with a minor allele frequency of < 1% (Table 2). The difference in the number of SNPs between the *IFITM1* and *IFITM3* genes indicates that the *IFITM1* gene is more relatively well conserved than the *IFITM3* gene. However, this result could also be influenced by ethnic features or small sample sizes; thus, further investigation is needed to confirm polymorphic characteristics of the *IFITM1* gene in larger and different ethnic groups.

We compared genotype, allele and haplotype frequencies of the *IFITM1* gene between healthy controls and pandemic influenza A 2009 H1N1 virus-infected patients and evaluated an association between the susceptibility to pandemic influenza A 2009 H1N1 virus infection and the *IFITM1* polymorphisms. Notably, there was no association between the susceptibility to pandemic influenza A 2009 H1N1 virus infection and *IFITM1* polymorphisms (Table 2). Previous studies have reported that the specificity of protection afforded by the IFITM3 protein against influenza A virus is higher than that for the IFITM1 protein, which may be the reason that no association between the susceptibility to pandemic influenza A 2009 H1N1 virus infection and *IFITM1* polymorphisms was observed (Perreira et al. 2013). However, we annotated *IFITM1* SNPs and found that 2 regulatory SNPs did not affect transcription factor-binding ability (Fig. 2). In addition, the remaining SNP did not disrupt splicing regulatory elements. Thus, since the *IFITM1* SNPs has been shown to have no effect on the phenotype of the *IFITM1* gene, nonfunctional *IFITM1* SNPs found in this study can also be responsible for the lack of association between the susceptibility to pandemic influenza A 2009 H1N1 virus infection and *IFITM1* polymorphisms. Further investigation of novel functional *IFITM1* polymorphisms can be helpful to confirm this interpretation in the future. We found a strong genetic linkage between *IFITM3* SNPs and *IFITM1* c.-416C > G SNP. However, the degree of strong genetic linkage is different between healthy controls and influenza A H1N1-infected patients and the genetic LD of pandemic influenza A H1N1-infected patients showed weaker than that of healthy controls (Tables 5, 6). Thus, the weak genetic linkage between *IFITM1* and *IFITM3* SNPs is associated with various genotypes of these two genes and may be related to the various phenotypes of these two genes. Further analysis is needed to elucidate the association between the degree of LD value and the susceptibility of pandemic influenza A H1N1 virus infection. In addition, although the *IFITM2* gene, another member of the IR-IFITM subfamily, is related to antiviral function, the IFITM2 protein showed a weaker antiviral effect than the IFITM3 protein in previous study (Perreira et al. 2013). Further study of the relationship between the susceptibility of the influenza H1N1 virus infection and *IFITM2* SNPs is highly desirable in the future.

In conclusion, we identified 3 novel SNPs of the *IFITM1* gene. In addition, we investigated the genotype, allele and haplotype frequencies of the *IFITM1* gene, analyzed the LD of this gene and evaluated an association between the susceptibility to pandemic influenza A 2009 H1N1 virus infection and the *IFITM1* polymorphisms. Furthermore, we analyzed the binding ability of transcription factors according to

Table 5 Linkage disequilibrium (LD) between single nucleotide polymorphisms (SNPs) of the *IFITM1* and *IFITM3* genes with r^2 values in the healthy controls

	IFITM3							*IFITM1*		
	c.-204G > T	c.-188T > C	c.-181T > C	c.-178A > C	c.-175T > C	c.42C > T	c.669T > C	c.-416C > G	c.-327A > C	c.186 + 18G > A
IFITM3										
c.-204G > T	–	–	–	–	–	–	–	–	–	–
c.-188T > C	0.145	–	–	–	–	–	–	–	–	–
c.-181T > C	0.478	0.085	–	–	–	–	–	–	–	–
c.-178A > C	0.469	0.084	0.983	–	–	–	–	–	–	–
c.-175T > C	0.469	0.084	0.983	1.0	–	–	–	–	–	–
c.42C > T	0.758	0.316	0.349	0.343	0.343	–	–	–	–	–
c.699T > C	0.039	0.192	0.019	0.019	0.019	0.048	–	–	–	–
IFITM1										
c.-416C > G	**0.422**	0.084	**0.851**	**0.866**	**0.866**	**0.321**	0.019	–	–	–
c.-327A > C	0.005	0.001	0.01	0.01	0.01	0.004	0	0.01	–	–
c.186 + 18G > A	0.005	0.001	0.01	0.01	0.01	0.004	0	0.01	0	–

Bold texts indicate strong LD between *IFITM1* SNP and *IFITM3* SNPs ($r^2 > 0.3$)

Table 6 Linkage disequilibrium (LD) between single nucleotide polymorphisms (SNPs) of the *IFITM1* and *IFITM3* genes with r^2 values in pandemic influenza A 2009 H1N1-affected individuals

	IFITM3							*IFITM1*		
	c.-204G > T	c.-188 T > C	c.-181 T > C	c.-178A > C	c.-175 T > C	c.42C > T	c.669 T > C	c.-416C > G	c.-327A > C	c.186 + 18G > A
IFITM3										
c.-204G > T	–	–	–	–	–	–	–	–	–	–
c.-188T > C	NA	–	–	–	–	–	–	–	–	–
c.-181T > C	0.932	NA	–	–	–	–	–	–	–	–
c.-178A > C	0.932	NA	1.0	–	–	–	–	–	–	–
c.-175T > C	0.932	NA	0.863	0.863	–	–	–	–	–	–
c.42C > T	NA	NA	NA	NA	NA	–	–	–	–	–
c.699T > C	NA	NA	NA	NA	NA	NA	–	–	–	–
IFITM1										
c.-416C > G	**0.536**	NA	**0.5**	**0.5**	**0.5**	NA	NA	–	–	–
c.-327A > C	NA	NA	NA	NA	NA	NA	NA	NA	–	–
c.186 + 18G > A	NA	NA	NA	NA	NA	NA	NA	NA	NA	–

Bold texts indicate strong LD between *IFITM1* SNP and *IFITM3* SNPs ($r^2 > 0.3$)

the alleles of the *IFITM1* SNPs and measured the LD values between the *IFITM1* and *IFITM3* genes. To the best of our knowledge, this report is the first association study between the susceptibility to pandemic influenza A 2009 H1N1 virus infection and *IFITM1* polymorphisms.

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Author contributions YCK, SYW and BHJ conceived and designed the experiments. YCK and SYW performed the experiments. YCK and BHJ analyzed the data. YCK, SYW and BHJ wrote the paper. All authors read and approved the final manuscript.

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

Ethical approval All procedures performed in the present study were accredited by the institutional review board of the Jeonbuk National University and were in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards (Approval number: JBNU 2017-08-009).

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