Molecular & Cellular Toxicology (2021) 17:51–57
https://doi.org/10.1007/s13273-020-00108-3

ORIGINAL ARTICLE

Genetic association between the rs12252 SNP of the interferon-induced transmembrane protein gene and influenza A virus infection in the Korean population

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Accepted: 21 October 2020 / Published online: 4 November 2020

Abstract

Background Interferon-induced transmembrane protein 3 (IFITM3) is a potent host antiviral effector protein that blocks the invasion of various viruses, including the influenza A virus (IAV). The C allele of the rs12252 single nucleotide polymorphism (SNP) shows vulnerability to the pandemic 2009 H1N1 IAV in European and Asian populations.

Objective Here, we estimated the disease susceptibility of the rs12252 SNP with the pandemic 2009 H1N1 IAV infection in the Korean population.

Results We carried out direct sequencing of the *IFITM3* gene and compared the genotype and allele frequencies of the rs12252 SNP of the *IFITM3* gene in healthy Koreans and pandemic 2009 H1N1 IAV-infected patients. Notably, we observed that healthy individuals had a similar genotype distribution of the rs12252 SNP ($P=0.140$) as patients. The dominant model and recessive model did not find a statistically significant difference in genotype distribution between healthy individuals and patients. In addition, the allele distribution of the rs12252 SNP of in healthy individuals and patients also showed a similar genetic distribution ($P=0.757$). However, the genetic distribution of rs12252 SNP in merged patient group (Koreans and Chinese populations) showed significant association with susceptibility of pandemic 2009 IAV ($P=0.0393$).

Conclusion To the best of our knowledge, this was the first evaluation of the susceptibility of the pandemic 2009 H1N1 IAV in the Korean population.

Keywords IFITM3 · Single nucleotide polymorphism · rs12252 SNP · Case–control study

Introduction

Interferon-induced transmembrane protein 3 (IFITM3) is a host antiviral effector protein that augments expression levels by type I and II interferons to respond to the invasion of various viruses, including influenza A virus (IAV) (Brass et al. 2009; Weidner et al. 2010; Bailey et al. 2012; Diamond and Farzan 2013; Kim et al. 2019; Lee et al. 2019). IFITM3 protein is localized in late endosomes and inhibits endosomal escape of influenza A viruses (Feeley et al. 2011). In particular, the N-terminal domain of the IFITM3 protein contains a sorting signal motif and plays a pivotal role in correct localization to the endosome and in blocking viral infections (Jia et al. 2012, 2014; Li et al. 2013).

Recent studies showed that single nucleotide polymorphisms (SNPs) of the *IFITM3* gene influence the antiviral capacity of the IFITM3 protein and are associated with the severity of the pandemic 2009 H1N1 IAV, which had a disastrous effect worldwide (van 't Klooster et al. 2010; Tramuto et al. 2011; Kim 2016). Among these SNPs, the C allele of the rs12252 SNP, which is located on the splicing receptor site, makes a 21 amino acid-shortened splicing isoform of the IFITM3 protein and shows susceptibility to the pandemic 2009 H1N1 IAV (Everitt et al. 2012). According to the 1000 genome database, although the European population has only 0.3% of the rs12252 SNP CC genotype,

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the CC genotype was found in 5.7% of hospitalized patients and showed a statistically significant association with the susceptibility to the pandemic 2009 H1N1 IAV. The correlation of the rs12252 SNP with the susceptibility to the severe pandemic 2009 H1N1 IAV was reaffirmed in Han Chinese populations, and there was a strong association between the number of intensive care unit patients and the rs12252 SNP CC genotype (Zhang et al. 2013; Lee et al. 2017). In addition, a case–control study in the Caucasian population identified an association of the rs12252 SNP with mild influenza infection (Mills et al. 2014). Previous study investigated the number of deaths from the pandemic 2009 H1N1 IAV and tried to find a correlation between the disease severity of influenza A virus infection and the rs12252 SNP; however, the study did not find an association of the rs12252 SNP with influenza severity (Kim and Jeong 2017). Although the relationship between influenza severity and rs12252 SNP was elusive (Lopez-Rodriguez et al. 2016), a cross-ethnic case–control study and a meta-analysis have validated the disease association of the rs12252 SNP with the pandemic 2009 H1N1 IAV (Xuan et al. 2015; Yang et al. 2015; Chen et al. 2018; Makvandi-Nejad et al. 2018; Prabhu et al. 2018). Several studies on ethnic groups have confirmed the relationship between the rs12252 SNP and the susceptibility to the pandemic 2009 H1N1 IAV, but an evaluation of the susceptibility to this virus in the Korean population has not been performed thus far.

In the present study, we estimated the disease susceptibility of the rs12252 SNP with the pandemic 2009 H1N1 IAV infection in the Korean population. For this, we carried out direct sequencing of the *IFITM3* gene and analyzed the genotype and allele frequencies of the rs12252 SNP of the *IFITM3* gene between healthy individuals and pandemic 2009 H1N1 IAV-infected patients in Korea.

Materials and methods

Subjects

Thirty blood samples of laboratory-confirmed pandemic 2009 H1N1 IAV-infected patients were provided from the Jeonbuk National University Hospital Biobank, a member of the Korea Biobank Network. A total of 204 blood samples from healthy Korean subjects were obtained from the Korea Biobank Network at the Centers for Disease Control and Prevention. All samples derived from the Korea Biobank Network were obtained with informed consent under institutional review board-approved protocols. The exclusion criteria of healthy Koreans included diabetes, high blood pressure, gastritis, gastric ulcer, myocardial infarction, thyroid disease, congestive heart failure, coronary artery disease, hypothyroidism asthma, chronic lung disease, peripheral vascular disease, kidney disease, hepatitis, tuberculosis, cerebrovascular disease, head trauma, urinary tract infection, arthritis and cancer. All the samples and related data were anonymized prior to the analysis.

Genomic DNA extraction

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

Amplification of the *IFITM3* gene and genetic analysis

The human *IFITM3* gene was amplified from genomic DNA using forward and reverse gene-specific primers. The sequences of the primers were as follows: IFITM3-F (5′-CAGGGGAAGTCTCCAGGACC-3′) and IFITM3-R (5′-CCAAGCCACACACACACACA-3′). Polymerase chain reaction (PCR) was performed 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 of IFITM3-F and IFITM3-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 S-1000 Thermal Cycler (Bio-Rad, Hercules, California, USA). The PCR products were purified using the PCR Purification Kit (Thermo Fisher Scientific, Bridgewater, New Jersey, USA) and directly sequenced with an ABI 3730 Automated Sequencer (ABI, Foster City, California, USA). Sequencing results were read by Finch TV software (Geospiza Inc, Seattle, Washington, USA), and genotyping was carried out.

Literature search

A literature search was conducted to looking for rs12252 SNP of the IFITM3 gene in previous studies. The searching terms were: "*IFITM3*", "SNP", "IAV" combined with "pandemic" or "susceptibility". Moreover, we supplemented our search by screening the reference lists of the relevant studies, including the original article. References for all identified publications were indicated in Table 2.

Genetic analysis

Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., USA). The differences in genotype and allele frequencies of the *IFITM3* gene between case and control populations compared using χ^2 test. The

Table 1 The detailed information of the study population

Characteristics	Cases	Controls
Number	30	204
Age	55.27 ± 17.88	62.43 ± 8.96
Sex (*n*, %)		
Male	11 (36.67)	74 (36.27)
Female	19 (63.33)	130 (63.73)

Hardy–Weinberg Equilibrium (HWE) test was performed using HWE calculator (https://www.genes.org.uk/software/hardy-weinberg.shtml).

Results

Subject description

A total of 234 individuals were included in the association analysis. Detailed information on the study population is described in Table 1. A total of 30 pandemic 2009 H1N1 IAV-diagnosed patients were composed of 19 females and 11 males. A total of 204 healthy individuals were composed of 130 females and 74 males. The mean age at diagnosis of 2009 H1N1 IAV-infected patients was 55.27 ± 17.88 years, and the mean age of healthy individuals at sample collection was 62.43 ± 8.96 years.

Genotyping and HWE analyses

We performed direct sequencing in 204 healthy individuals and 30 pandemic 2009 H1N1 IAV-infected patients and carried out genotyping and HWE analyses. Detailed information on the genotyping results and HWE values in the Korean population is described in Table 2.

Evaluation of susceptibility of H1N1 influenza 2009 pandemic virus infection in the Korean population

To estimate disease the susceptibility of the rs12252 SNP of the *IFITM3* gene with the pandemic 2009 H1N1 IAV in the Korean population, we performed a case–control association study. We observed that healthy individuals had a similar genotype distribution of the rs12252 SNP ($P = 0.1403$) to patients in the Korean population. Among 16 groups investigated in previous studies, the healthy Han Chinese population has a most similar distribution of rs12252 SNP with the healthy Korean population in genotype ($P = 0.4442$) and allele ($P = 0.2119$) frequencies (Table 2). We additionally tried to analyze association using the dominant model and recessive model in the Korean population.

Analyses in dominant and recessive models

To find risk factor on the susceptibility of pandemic 2009 H1N1 IAV infection in Korean population, two genetic models, including dominant and recessive models were performed in this study. In dominant model, the distribution of CC + CT and TT genotypes is 163 (79.9%) and 41 (20.1%) in control and 28 (93.3%) and 2 (6.7%) in case, respectively. The frequency of the CC + CT genotypes in pandemic 2009 H1N1 IAV-infected patients is substantially greater than that in the normal Korean population. However, the dominant model ($P = 0.076$) and the recessive model ($P = 0.757$) did not find a statistically significant difference in the genotype distribution between healthy individuals and patients (Table 3). In addition, the allele distribution of the rs12252 SNP in healthy individuals and patients also showed a similar genetic distribution ($P = 0.437$, Table 2).

Discussion

In the present study, we estimated the susceptibility of the rs12252 SNP to the pandemic 2009 H1N1 IAV in the Korean population. Interestingly, all genetic models performed in this study showed no correlation between the rs12252 SNP and the susceptibility of the pandemic 2009 H1N1 IAV in the Korean population. Further research is needed to assess whether this result is due to ethnic background. In addition, because it can be triggered by the small sample size of pandemic 2009 H1N1 IAV-infected patients in the Korean population, further study in a large population should be performed to validate the correlation between the rs12252 SNP and the susceptibility of the pandemic 2009 H1N1 IAV in the Korean population. However, there are severe limitations in this study due to small sample numbers of pandemic 2009 H1N1 IAV-infected patients and the impossibility of stratified study according to disease severity under current status of Korea biobank. Sample collection is systematically needed at the national level for preemptive control of pandemic diseases. Indeed, the mechanism of the antiviral capacity of the rs12252 SNP is elusive. Previous in vivo and in vitro studies failed to detect the 21 amino acid-shortened splicing isoform of the IFITM3 protein induced by the rs12252 SNP C allele (Makvandi-Nejad et al. 2018).

In recent a study, the rs34481144 SNP, which is located on the promoter of the *IFITM3* gene, showed an association with the severity of the pandemic 2009 H1N1 IAV (Allen et al. 2017; David et al. 2018). The rs34481144 SNP potently influenced the host innate immune system by modulating not only the expression level of the *IFITM3*

Table 2 Genotype and allele frequencies of rs12252 SNP in healthy individuals and pandemic 2009 H1N1 Influenza A virus (IAV) affected patients in several populations

Year	Populations		Total	Genotype frequency, *n* (%)			*P* value[a]	*P* value[b]	Allele frequency, *n* (%)		*P* value[c]	*P* value[d]	HWE	Ref
				CC	CT	TT			C	T				
Control														
2012	YRI[e]		59	1 (1.7)	9 (15.3)	49 (83)	< 0.0001	< 0.0001	11 (9.3)	107 (90.7)	< 0.0001	< 0.0001	0.4530	Everitt et al. (2012)
2012	CHB[f]/JPT[g]		60	9 (15)	18 (30)	33 (55)	< 0.0001	< 0.0001	36 (30)	84 (70)	< 0.0001	< 0.0001	0.0269	
2012	CEU[h]/FIN[i]/GBR[j]/IBS[k]/TSI[l]		360	1 (0.3)	24 (6.7)	335 (93)	< 0.0001	< 0.0001	26 (3.6)	694 (96.4)	< 0.0001	< 0.0001	0.4218	
2013	United Kingdom		89	0 (0)	2 (2.2)	87 (97.8)	< 0.0001	< 0.0001	2 (1.1)	176 (98.9)	< 0.0001	< 0.0001	0.9146	Zhang et al. (2013)
2013	Northern Europe		87	0 (0)	7 (8.1)	80 (91.9)	< 0.0001	< 0.0001	7 (4)	167 (96)	< 0.0001	< 0.0001	0.6958	
2013	Japanese		89	39 (43.8)	35 (39.3)	15 (16.9)	**0.0553**	0.0420	113 (63.5)	65 (36.5)	**0.0470**	0.6296	0.1521	
2013	Han Chinese		197	50 (25.4)	98 (49.7)	49 (24.9)	**0.4442**	0.0515	198 (50.3)	196 (49.7)	**0.2119**	0.1594	0.9435	
2014	GRACE[m] Control		2623	4 (0.2)	202 (7.7)	2417 (92.1)	< 0.0001	< 0.0001	210 (4)	5036 (96)	< 0.0001	< 0.0001	0.9178	Mills et al. (2014)
2016	Spanish		246	0 (0)	17 (6.9)	229 (93.1)	< 0.0001	< 0.0001	17 (3.5)	475 (96.5)	< 0.0001	< 0.0001	0.5746	López-Rodríguez et al. (2016)
2017	China		208	47 (22.6)	105 (50.5)	56 (26.9)	**0.1437**	0.0353	199 (47.8)	217 (52.2)	**0.0502**	0.0781	0.8682	Lee et al. (2017)
2018	East Asian		286	86 (30.1)	109 (38.1)	91 (31.8)	0.0058	0.0021	281 (49.1)	291 (50.9)	0.0877	0.1090	< 0.0001	David et al. (2018)
2018	Europe		379	0 (0)	26 (6.9)	353 (93.1)	< 0.0001	< 0.0001	26 (3.4)	732 (96.6)	< 0.0001	< 0.0001	0.4893	
2018	IBS		14	0 (0)	0 (0)	14 (100)	< 0.0001	< 0.0001	0 (0)	28 (100)	< 0.0001	< 0.0001	NA[p]	
2018	PGP[n]		200	0 (0)	24 (12)	176 (88)	< 0.0001	< 0.0001	24 (6)	376 (94)	< 0.0001	< 0.0001	0.3667	
2018	Africa		246	15 (6.1)	89 (36.2)	142 (57.7)	< 0.0001	< 0.0001	119 (24.2)	373 (75.8)	< 0.0001	< 0.0001	0.8324	
2018	Central Africa		148	10 (6.8)	58 (39.2)	80 (54)	< 0.0001	< 0.0001	78 (26.4)	218 (73.6)	< 0.0001	< 0.0001	0.9066	
–	Korea		204	60 (29.4)	103 (50.5)	41 (20.1)	–	0.1403	223 (54.7)	185 (45.3)	–	0.4370	0.7901	In this study
Case														
2012	England and Scotland	Total	53	3 (5.7)	4 (7.5)	46 (86.8)	< 0.0001	< 0.0001	10 (9.4)	96 (90.6)	< 0.0001	< 0.0001	< 0.0001	Everitt et al. (2012)
2013	China	Total	83	35 (42.2)	39 (47)	9 (10.8)	0.0511	**0.1993**	109 (65.7)	57 (34.3)	0.0155	0.4331	0.7019	Zhang et al. (2013)
		Severe	32	22 (68.8)	8 (25)	2 (6.2)	0.0001	0.0017	52 (81.3)	12 (18.7)	< 0.0001	0.0092	0.3099	
		Mild	51	13 (25.5)	31 (60.8)	7 (13.7)	0.3825	0.7374	57 (55.9)	45 (44.1)	0.8239	0.6088	0.0965	

Table 2 (continued)

Year	Populations		Total	Genotype frequency, *n* (%)			*P* value[a]	*P* value[b]	Allele frequency, *n* (%)		*P* value[c]	*P* value[d]	HWE	Ref
				CC	CT	TT			C	T				
2014	GAinS[o] and GRACE	Total	293	2 (0.7)	25 (8.5)	266 (90.8)	< 0.0001	< 0.0001	29 (4.9)	557 (95.1)	< 0.0001	< 0.0001	0.1112	Mills et al. (2014)
		Severe	34	0 (0)	3 (8.8)	31 (91.2)	< 0.0001	< 0.0001	3 (4.4)	65 (95.6)	< 0.0001	< 0.0001	0.7878	
		Mild	259	2 (0.8)	22 (8.5)	235 (90.7)	< 0.0001	< 0.0001	26 (5)	492 (95)	< 0.0001	< 0.0001	0.0790	
2016	Spanish	Total	152	1 (0.7)	18 (11.8)	133 (87.5)	< 0.0001	< 0.0001	20 (6.6)	284 (93.4)	< 0.0001	< 0.0001	0.6516	López-Rodríguez et al. (2016)
		Severe	34	0 (0)	5 (14.7)	29 (85.3)	< 0.0001	< 0.0001	5 (7.4)	63 (92.6)	< 0.0001	< 0.0001	0.6435	
		Mild	118	1 (0.9)	13 (11)	104 (88.1)	< 0.0001	< 0.0001	15 (6.4)	221 (93.6)	< 0.0001	< 0.0001	0.4183	
2017	China	Total	224	84 (37.4)	89 (39.9)	51 (22.7)	0.0749	0.0141	257 (57.4)	191 (42.6)	0.4251	0.6982	0.0050	Lee et al. (2017)
		Severe	23	13 (56.5)	6 (26.1)	4 (17.4)	0.0309	0.0146	32 (69.6)	14 (30.4)	0.0534	0.3088	0.0656	
		Mild	201	70 (35)	84 (41.7)	47 (23.3)	0.2137	0.0236	224 (55.7)	178 (44.3)	0.7607	0.5331	0.0300	
2018	Portuguese	Total	41	1 (2.5)	6 (14.6)	34 (82.9)	< 0.0001	< 0.0001	8 (9.8)	74 (90.2)	< 0.0001	< 0.0001	0.2794	David et al.(2018)
		Severe	22	0 (0)	4 (18.2)	18 (81.8)	< 0.0001	< 0.0001	4 (9.1)	40 (90.9)	< 0.0001	< 0.0001	0.6390	
		Mild	19	1 (5.3)	2 (10.5)	16 (84.2)	< 0.0001	< 0.0001	4 (10.5)	34 (89.5)	< 0.0001	< 0.0001	0.0545	
–	Korea	Total	30	8 (26.7)	20 (66.6)	2 (6.7)	0.1403	–	36 (60)	24 (40)	0.4370	–	0.0332	In this study
		Severe	1	1 (100)	0 (0)	0 (0)	0.4976	0.3548	2 (100)	0 (0)	0.5035	0.5177	NA	
		Mild	29	7 (24.1)	20 (69)	2 (6.9)	0.1314	1.0	34 (58.6)	24 (41.4)	0.5701	0.8788	0.0232	

P value[a]: based on comparison of genotype frequencies with Korean control population

P value[b]: based on comparison of genotype frequencies with Influenza A(H1N1) pdm09 Korean patients

P value[c]: based on comparison of allele frequencies with Korean control population

P value[d]: based on comparison of allele frequencies with Influenza A(H1N1) pdm09 Korean patients

YRI[e]: Yoruba in Ibadan, Nigeria (African)

CHB[f]: Han Chinese in Beijing, China

JPT[g]: Japanese in Tokyo, Japan

CEU[h]: Utah residents with Northern and Western European ancestry from the CEPH collection (European)

FIN[i]: Finns

GBR[j]: British

IBS[k]: IBERIAN populations in Spain

TSI[l]: Toscani

GRACE[m]: genomics to combat resistance against antibiotics in community acquired LRTI in Europe

PGP[n]: Portuguese general population

GAinS[o]: genomic advances in sepsis

NA[p]: not applicable

Table 3 Association analysis in the dominant and recessive models in Korean population

Genetic model	Control	Case	*P* value
Dominant model, *n* (%)			
CC + CT	163 (79.9)	28 (93.3)	0.076
TT	41 (20.1)	2 (6.7)	
Recessive model, *n* (%)			
CC	60 (29.4)	8 (26.7)	0.757
CT + TT	144 (70.6)	22 (73.3)	
Total, *n*	204	30	

gene but also those of neighboring genes (Allen et al. 2017). In addition, the rs6598045 SNP was associated with the binding ability of the transcription factor of the *IFITM3* gene and related to the susceptibility of the pandemic 2009 H1N1 IAV. T allele of rs6598045 SNP which is more prevalent in 2009 pandemic influenza-infected patients showed reduced promoter activity compared to C allele of rs6598045 which is more prevalent in healthy control (Kim et al. 2020). Because of the close genetic locus among the three SNPs, including rs12252 SNP, rs34481144 SNP and rs6598045 SNP, investigation of the relationship among them is highly desirable in the future.

In conclusion, we investigated the genotype and allele frequencies of the rs12252 SNP of the *IFITM3* gene and estimated the susceptibility of the pandemic 2009 H1N1 IAV in the Korean population. We found no correlation between the genotype, allele and dominant and recessive models of the rs12252 SNP and the vulnerability of the pandemic 2009 H1N1 IAV in the Korean population. To the best of our knowledge, this was the first evaluation of the susceptibility of the pandemic 2009 H1N1 IAV in the Korean population.

Acknowledgements The biospecimens and data used in this study were provided by the Biobank of Jeonbuk National University Hospital, a member of the Korea Biobank Network, which is supported by the Ministry of Health, Welfare and Family Affairs. All samples derived from the Korea Biobank Network were obtained with informed consent under institutional review board-approved protocols. This research was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (2017R1A6A1A03015876). This research was supported by the Basic Science Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (2018R1D1A1B07048711). This research was supported by "Research Base Construction Fund Support Program" funded by Jeonbuk National University in 2020. Min-Ju Jeong was supported by the BK21 Plus Program in the Department of Bioactive Material Sciences. This work was supported by NRF (National Research Foundation of Korea) Grant funded by the Korean Government (NRF-2019-Fostering Core Leaders of the Future Basic Science Program/Global Ph.D. Fellowship Program). This work was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (2020R1A6A3A1307432311). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Author contributions Y.C. Kim, M.J. Jeong and B.H. Jeong conceived and designed the experiments. Y.C. Kim and M.J. Jeong performed the experiments. Y.C. Kim and B.H. Jeong analyzed the data. Y.C. Kim, M.J. Jeong and B.H. Jeong 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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