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LETTER TO THE EDITOR

Minor Allele of Interferon-Induced Transmembrane Protein 3 Polymorphism (rs12252) Is Covered Against Severe Acute Respiratory Syndrome Coronavirus 2 Infection and Mortality: A Worldwide Epidemiological Investigation

To the Editor—The recent article by Zhang et al [1] described the genetic association of interferon-induced transmembrane protein 3 (IFITM3) with severe coronavirus disease 2019 (COVID-19). Eighty Chinese subjects infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were recruited and genotyped for the IFITM3 rs12252 gene polymorphism. The authors revealed an age-dependent association of severe COVID-19 in the studied Chinese cohort. Furthermore, subjects harboring the CC genotype had a 6.37-fold higher risk of severe pathogenesis when infected with SARS-CoV-2. These observations encouraged us to investigate the association of the IFITM3 rs12252 polymorphism with susceptibility to SARS-CoV-2 infection and mortality in the worldwide population.

For COVID-19–related worldwide data, we explored the Worldometer website (https://www.worldometers.info/coronavirus/) and extracted data such as country name, number of cases per million, and the number of deaths per million population due to SARS-CoV-2 infections (accessed 10 August 2020). The prevalence of IFITM3 rs12252 genotypes or alleles in different countries was searched through the PubMed database. All relevant publications were inspected, and authors' details, country name, IFITM3 genotypes, and allele number or frequency of healthy controls were obtained. Reports containing genotype distributions not following Hardy–Weinberg equilibrium (HWE) were excluded from the present study.

The data search on 10 August 2020 revealed the presence of SARS-CoV-2 infection in 215 countries comprising 20 million cases and >0.7 million deaths worldwide. Out of 215 countries, IFITM3 rs12252 polymorphism data were available for 23 countries. The mutant allele (C) ranges from 3.27% to 63.48%.

As the distribution of IFITM3 rs12252 genotypes deviated from HWE in 4 studies from Chinese populations and 1 study each from Vietnam and Iran, these were excluded from the present study. A total of 21 countries were considered for the present analysis (Table 1). Spearman rank correlation analysis revealed an inverse correlation between the SARS-CoV-2 infection rate per million population and the IFITM3 rs12252 minor allele (C) (r = –0.632; P = .002; n = 21) (Table 1). A good healthcare system is believed to minimize the death rate due to SARS-CoV-2 infection. Thus, for analysis of the possible correlation between mortality rate and IFITM3 rs12252 polymorphism, data of 3 countries (Bangladesh, Pakistan, and Sri Lanka) were excluded as those countries spend <3% of their gross domestic product in the health sector. Interestingly, the C allele of IFITM3 rs12252 polymorphism was negatively correlated with the SARS-CoV-2 mortality rate per million (r = –0.715; P = .0008; n = 18) (Table 1).

Zhang et al [1] have demonstrated a significant association of the rs12252-CC genotype with severe COVID-19, most frequently in Chinese patients who died from SARS-CoV-2 infection. In contrast, we observed a beneficial effect of allele C against SARS-CoV-2 infection and related mortality in worldwide populations. Similar to our observation, a recent preprint report in different ethnic groups of England's population described a positive correlation of the rs12252 dominant allele with SARS-CoV-2–related death [2]. The reasons for these discrepancies are not known. It is believed that the rs12252-CC genotype produces a truncated variant of 21 amino acids at the N-terminal region of the protein, which leads to loss of antiviral activity. Earlier reports in the Chinese population have demonstrated a significant association of the rs12252-C allele with severity of influenza infection but failed to exhibit such a link in Korean, American, African American, European, and Brazilian cohorts [3]. Furthermore, some reports also failed to detect the presence of truncated IFITM3 isoform in RNAseq data of subjects carrying the rs12252-CC genotype [4, 5]. These observations indicate the possibility of other functional variants in the IFITM3 gene on the determination of the clinical phenotype of viral infections.

A single-nucleotide polymorphism in the 5′ untranslated region of the IFITM3 gene rs34481144 (G > A) has been shown to alter IFITM3 levels in peripheral blood mononuclear cells [6]. Diminished production of IFITM3 messenger RNA is linked with the minor allele A by decreased IRF3 and increased CTCF binding capability [6]. As the number of reports on the prevalence of rs34481144 polymorphism is limited worldwide, we were unable to investigate the possible association of rs34481144 with COVID-19. Distribution of rs12252 and rs3448114 polymorphisms always follows opposite trends: A population with a higher rs12252-C incidence has a lower prevalence of rs3448114-G, and vice-versa. Furthermore, the recessive genotype of both polymorphisms was never inherited together. Based on the results of the present study and other observations, it can be presumed that the minor allele of rs3448114 polymorphism could be positively linked with SARS-CoV-2 susceptibility and mortality. However, further case-control studies in different ethnic groups, including larger sample sizes, are required to validate our observations and to obtain an accurate inference on the role of the IFITM3 gene in the pathogenesis of COVID-19.

Table 1. Details of Coronavirus Disease 2019 Data, IFITM3 rs12252 Genotype Prevalence, and Correlation Analysis

Country	SARS-CoV-2–Infected Cases per Million Population	SARS-CoV-2–Related Deaths per Million Population	No. of Reports Considered for Prevalence of Genotype Investigation	Total No. of Healthy Controls	C/C Genotype, No.	C/T Genotype, No.	T/T Genotype, No.	C Allele, No.	T Allele, No.	Frequency of Allele C, %	References	No. of Doctors/10 000 Population	No. of Nurses/10 000 Population	Expenditure of % of GDP on Health Sector	Spearman Rank Correlation
Nigeria	48	3	3	266	18	89	159	125	407	23.49	Jiménez et al 2017; Kim et al 2017	3.81	11.79	3.7	Allele C frequency (%) vs SARS-CoV-2 cases/million (r = –0.632, P = .002, n = 21); Allele C frequency (%) vs deaths/million (r = –0.715, P = .0008, n = 18)
Kenya	491	8	1	99	8	43	48	59	139	29.79	Jiménez et al 2017	1.57	11.66	5.7	
The Gambia	510	9	1	113	8	33	72	49	177	21.68	Jiménez et al 2017	1.02	15.45	7.3	
Sierra Leone	240	9	1	85	5	32	48	42	128	24.70	Jiménez et al 2017	.25	2.24	11.1	
China	59	3	9	1383	351	687	345	1389	1377	50.21	Wang et al 2013; Zhang et al 2013; Lee et al 2017; Zhang et al 2013; Lee et al 2017; Pan et al 2017; Zhang et al 2013; Zhang et al 2015	19.8	26.62	5.5	
India	1603	32	2	205	5	45	155	55	355	13.41	Jiménez et al 2017	8.57	17.27	4.7	
South Korea	285	6	2	858	294	434	130	1022	694	59.55	Kim et al 2017; Seo et al 2010	23.61	73.01	7.4	
Japan	370	8	1	89	39	35	15	113	65	63.48	Kim et al 2017	24.12	121.5	10.2	
Spain	7730	610	3	599	0	41	558	41	1157	3.42	Rodríguez et al 2016; Jiménez et al 2017	38.72	57.3	9	
Finland	1369	60	1	99	0	16	83	16	182	8.08	Jiménez et al 2017	38.12	147.4	9.7	
Italy	4145	582	1	107	0	7	100	7	207	3.27	Jiménez et al 2017	39.77	57.4	9.2	
Portugal	5167	172	3	1086	2	132	952	136	2036	6.26	Gaio et al 2016; David et al 2017	51.24	69.75	9.5	
UK	4576	686	3	3072	5	228	2839	238	5906	3.87	Mills et al 2013; Everitt et al 2013; Kim et al 2017	28.12	81.72	9.1	
Mexico	3721	405	5	820	24	248	548	296	1344	18.04	Jiménez et al 2017	23.83	23.96	6.3	
US	15 698	500	5	10 642	10	701	9931	721	20 563	3.38	Carter et al 2017; Randolph et al 2017; Jiménez et al 2017	26.12	145.5	17.1	
Barbados	249	24	1	96	4	35	57	43	149	22.39	Jiménez et al 2017	24.84	30.6	7.5	
Colombia	7607	252	1	94	0	14	80	14	174	7.44	Jiménez et al 2017	21.85	13.31	7.2	
Peru	14 477	638	1	85	9	40	36	58	112	34.11	Jiménez et al 2017	24.4	13.05	5.5	
Bangladesh	1562	21	1	86	3	22	61	28	144	16.27	Jiménez et al 2017	5.81	4.12	2.8	
Pakistan	1286	28	1	96	5	24	67	34	158	17.70	Jiménez et al 2017	9.8	6.68	2.68	
Sri Lanka	133	.5	1	102	2	23	77	27	177	13.23	Jiménez et al 2017	10.04	21.8	3.5	

Data on SARS-CoV-2–infected cases, related death, and recovery rate were obtained from https://www.worldometers.info/coronavirus/ (accessed 10 August 2020). Correlation analysis was performed by Spearman rank correlation coefficient in GraphPad Prism 8.3.0 software.

Abbreviations: GDP, gross domestic product; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; UK, United Kingdom; US, United States.

Notes

Potential conflicts of interest. All authors: No reported conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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