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Coronavirus Pandemic

Angiotensin-converting enzyme 2 G8790A polymorphisms are associated with COVID-19 severity

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Abstract

Introduction: In order to prevent COVID-19 from progressing, angiotensin-converting enzyme 2 (ACE2) binds to SARS-CoV-2 and prevents the virus from entering target cells. Several studies have found a correlation between COVID-19 risk and the *ACE2* G8790A polymorphism; nevertheless, it remains inconclusive. A meta-analysis with relevant articles was carried out to more accurately estimate the risk of COVID-19.

Methodology: We conducted a systematic review using PubMed, Embase, Cochrane Library, Scopus, Science Direct and Web of Science databases. The odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. A meta-package was adopted in STATA version 12.0.

Results: It was concluded that the *ACE2* G8790A polymorphism was not associated with COVID-19 based on the data collected. Moreover, subgroup analyses stratified based on race proved that the *ACE2* G allele showed association with increasing risk of COVID-19 severity in Asians (G vs A: OR = 4.07, 95% CI = 3.19-5.19; GG vs AA: OR = 10.01, 95% CI = 5.39-18.56; GA vs AA: OR = 3.57, 95% CI = 1.84-6.93; dominant model: OR = 8.05, 95% CI = 4.36-14.88; recessive model: OR = 3.83, 95% CI = 2.89-5.08).

Conclusions: The findings indicated that the G allele of *ACE2* G8790A was related to an enhanced risk of COVID-19 severity in Asians. One possible reason is that *ACE2* G allele was associated with a COVID-19 cytokine storm. Furthermore, Asians have higher levels of *ACE2* transcripts than Caucasians and Africans. Therefore, a genetic factor should be considered when developing vaccines in the future.

Key words: ACE2; COVID-19; gene; polymorphism; risk.

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Introduction

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This disease was detected in China in late 2019 and developed into a pandemic in March 2020. Thereafter it caused a major public health problem worldwide [1]. Infection and severity of COVID-19 are linked to a variety of factors, including age of the patients, obesity, diabetes, and coronary heart disease [2]. In spite of extensive research, there is paucity of scientific explanation for why some individuals become infected while others remain uninfected when exposed to SARS-CoV-2.

In addition to its role as a receptor for SARS-CoV-2, full-length angiotensin-converting enzyme 2 (*ACE2*) is a transmembrane zinc-metalloproteinase type I protein with a size of 120-KDa. It contains a 17 amino acid signal peptide, and a collectrin-like domain at the C-terminus [3]. It can be found in two states, open and closed. The open state of *ACE2* is characterized by a wide opening from its active site which awaits the entrance of a ligand. As soon as the ligand enters the active site of *ACE2*, the active slot of *ACE2* is closed. A significant amount of *ACE2* is expressed in a number of tissues, with the highest levels of expression occurring in lungs, colon, and heart [4]. A second form of ACE2 with 555 amino acids circulates in a small amount in the blood, and is known as soluble ACE2. A full-length ACE2 is obtained by shedding of ADAM17. The binding of ACE2 to SARS-CoV-2 prevents the virus from entering the target cells, thereby preventing COVID-19 from progressing. In addition, ACE2 contributes to the absorption of neutral amino acids in the gut by serving as a protective factor in the cardiovascular system and other organs [5].

Researchers have investigated several single nucleotide polymorphisms (SNPs) associated with the *ACE2* gene as risk factors for hypertension and heart failure. The polymorphisms are on chromosome Xp22, G8790A (SNP rs2285666) and includes an A to G change at nucleotide +4 of intron 3 [6]. Since ACE2 is located on chromosome X, male carriers of alleles linked to *ACE2* expression are at a disadvantage. In addition, since *ACE2* is located on the X chromosome, the presence of alleles conferring resistance to SARS-CoV-2 has been suggested as a mechanism behind the

apparent lower female mortality rate [7]. Men have higher levels of *ACE2* expression in the lungs than women [8]. This may explain the higher prevalence of severe COVID-19 among males. *ACE2* expression is downregulated in myocardium by SARS-CoV resulting in an adverse effect on the heart due to inflammation and damage to the myocardium.

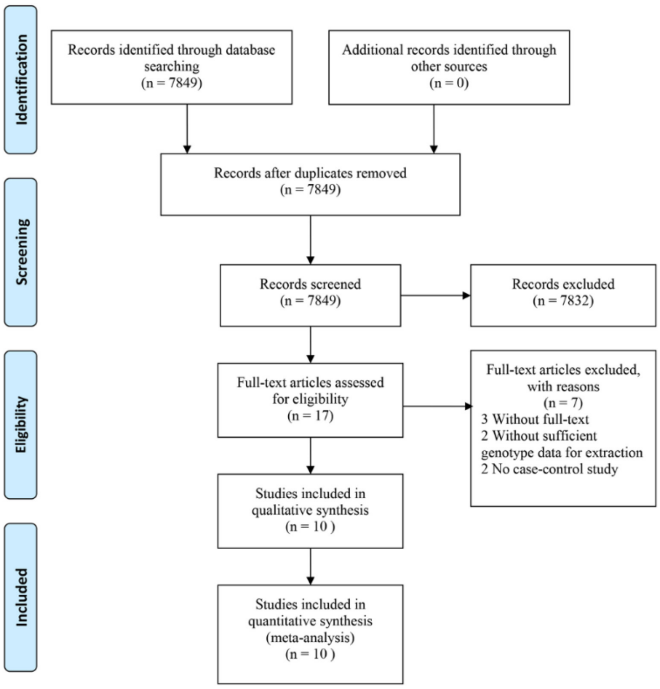
COVID-19 has been associated with the G8790A polymorphism in *ACE2* in multiple epidemiological studies in the past three years [9,10]. However, some studies have produced inconsistent results [11-14]. Using meta-analyses is an efficient method of detecting relationships that may not be apparent from small studies, particularly when there is an unusual allele frequency polymorphism to be evaluated. By using genetic profiling, early identification of people prone to severe COVID-19 may be possible, thereby preventing severe COVID-19.

Methodology

Study search strategy

A meta-analysis was conducted independently based on the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines. Articles examining the association between *ACE2* G8790A polymorphism and COVID-19 risk were retrieved from PubMed, Embase, Cochrane Library, Scopus, Science Direct and Web of Science using the keywords "angiotensin-converting enzyme 2" or "ACE2" and COVID-19 and "polymorphism" or "mutation" or "genotype" or "allele" or "variation" or "variant". In addition, all references in related studies were manually searched to avoid omissions. Literature retrieval was not restricted by language.

Figure 1. The flow diagram of included/excluded studies.



Inclusion and exclusion criteria

In order to extract appropriate information, research studies were selected using the following inclusion criteria: (1) Research examining the relationship between the *ACE2* G8790A polymorphism and the COVID-19, (2) Case-control studies, (3) Those whose genotyping data are available. However, research studies not related to COVID-19 and with missing data were excluded from the study.

Data extraction

The data extracted from individual studies included the following: first author, region, publication year, number of cases and controls, genotype frequencies, and the Hardy-Weinberg equilibrium (HWE).

In-silico analysis

The expression quantitative trait locus (eQTL) data from GTEx (https://gtexportal.org/home/) were extracted to examine the effect of G8790A polymorphism on *ACE2* gene expression [7]. Moreover, bioinformatics analysis was performed using the HaploReg website version 4.1 (http://pubs.broadinstitute.org/mammals/haploreg/haploreg.php) to predict ACE2 G8790A polymorphism function [7].

Statistical methods

STATA 12.0 was used for the meta-analysis. A correlation between the *ACE2* G8790A polymorphism and COVID-19 susceptibility was evaluated using odds ratios and their associated 95% CIs in different comparisons, including G vs A, homozygote (GG vs AA), heterozygote (GA vs AA), dominant model (GG+GA vs AA) and recessive model (GG vs GA+AA) between groups. In addition, HWE was calculated for genotype distribution among all enrolled research. In order to analyze heterogeneity, the I^2 statistic was used, and a value of $I^2 > 50\%$ indicated heterogeneity. A subgroup analysis based on ethnicity was also conducted. Additionally, this study conducted a sensitivity analysis by removing one study at a time. The exclusion of one study resulted in an estimation beyond 95% CI of the pooled analysis because of excessive sensitivity. A potential publication bias was also evaluated by Begg's funnel plot.

Results

Eligible studies

A total of 7849 relevant studies were identified, of which 10 articles were eligible for inclusion in this meta-analysis according to the above study criteria [9-19]. Among the articles included were those published between 2020 and 2022. A flow chart of the article selection process is presented in Figure 1. English language was used for all enrolled articles and the HWE test was used to determine the genotype distribution among controls. A summary of the study characteristics and relevant information of the included articles is shown in Tables 1 and 2.

Results of meta-analysis

Figure 2 and Table 3 present the correlation between *ACE2* G8790A polymorphism and the risk of COVID-19. Based on our results, *ACE2* G8790A polymorphism did not present any obvious relation with COVID-19 susceptibility with the use of diverse genetic models (G vs A: OR = 0.94, 95% CI = 0.55-1.60; GG vs AA: OR = 0.78, 95% CI 0.35-1.76; GA vs AA: OR = 0.56, 95% CI 0.25-1.29; dominant model: OR = 0.73, 95% CI = 0.33-1.61; recessive model: OR =1.05, 95% CI = 0.65-1.70). Race-stratified subgroup analysis concluded that *ACE2* G8790A polymorphism did not show any relation with COVID-19 risk among Caucasian or Asian Population.

The World Health Organization (WHO) guideline for the definition of disease severity was utilized to

Figure 2. Forest plot for meta-analysis of the association between the ACE2 G8790A polymorphism and COVID-19 risk.

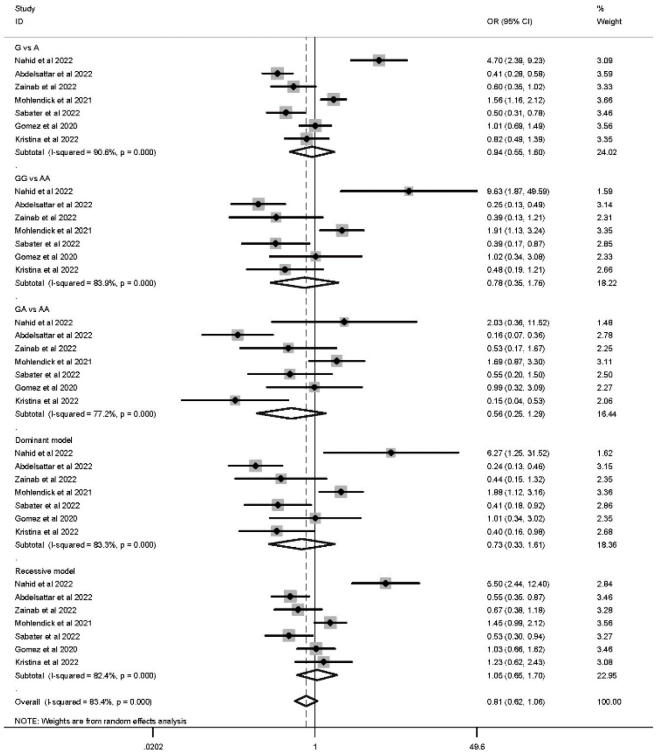


Table 1. The studies of ACE2 G8790A polymorphism with COVID-19 included in our analysis.

Study	Year	Country	Race	Cases / Controls	Allele for cases		Allele for controls		Genotypes for cases			Genotypes for controls			HWE
					G	A	G	A	GG	GA	AA	GG	GA	AA	
Nahid	2022	Iran	Asian	79/50	143	15	67	33	66	11	2	24	19	7	0.320
Abdelsattar	2022	Egypt	Caucasian	299/147	414	184	249	45	196	22	81	114	21	12	0.001
Zainab	2022	Iraq	Asian	99/96	104	44	115	29	51	37	11	59	32	5	0.808
Mohlendick	2021	Germany	Caucasian	297/253	500	94	391	115	230	40	27	178	35	40	0.001
Sabater	2022	Spain	Caucasian	213/95	316	110	162	28	142	32	39	75	12	8	0.001
Gomez	2020	Spain	Caucasian	125/248	202	48	400	96	82	38	5	161	77	10	0.835
Kristina	2022	Slovenia	Caucasian	68/96	103	33	152	40	49	5	14	65	22	9	0.003

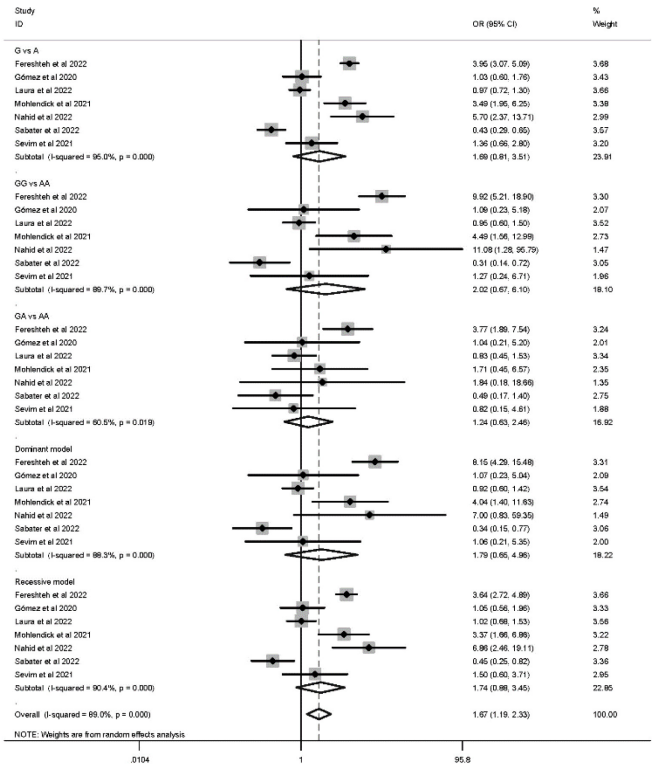
HWE: Hardy-Weinberg Equilibrium.

Table 2. The studies of ACE2 G8790A polymorphism with COVID-19 severity.

Study	Year	Country	Race	Severe / Mild	Allele for cases		Allele for controls		Genotypes for cases			Genotypes for controls			HWE
					G	A	G	A	GG	GA	AA	GG	GA	AA	
Fereshteh	2022	Iran	Asian	522/556	954	90	810	302	443	68	11	337	136	83	0.001
Gómez	2020	Spain	Caucasian	53/248	86	20	400	96	35	16	2	161	77	10	0.835
Laura	2022	Mexico	Caucasian	125/356	146	104	421	291	63	20	42	178	65	113	0.001
Mohlendick	2021	Germany	Caucasian	90/253	166	14	391	115	80	6	4	178	35	40	0.001
Nahid	2022	Iran	Asian	44/50	81	7	67	33	38	5	1	24	19	7	0.320
Sabater	2022	Spain	Caucasian	140/95	150	130	138	52	88	22	30	75	12	8	0.001
Sevim	2021	Turkey	Caucasian	91/24	37	12	127	56	14	8	2	44	39	8	0.877

define non-severe and severe cases [20]. Severe cases were those who had positive result in COVID-19 RT-PCR test, presented with clinical signs and severe pneumonia as well as severe respiratory distress, or SpO_2 < 90% in room air. Seven articles met the severe case criteria. Clearly, *ACE2* G8790A polymorphism was not related to the severity of COVID-19 (Figure 3 and Table 4, G vs A: OR = 1.69, 95% CI = 0.81-3.51; GG vs AA: OR = 2.02, 95% CI = 0.67-6.10; GA vs AA: OR = 1.24, 95% CI = 0.63-2.46; dominant model: OR = 1.79, 95% CI = 0.65-4.96; recessive model: OR = 1.74, 95% CI = 0.88-3.45). Based on subgroup analysis stratified by race, *ACE2* G8790A polymorphism was related to COVID-19 severity in Asians (Figure 4 and Table 4, G vs A: OR = 4.07, 95% CI = 3.19-5.19; GG vs AA: OR = 10.01, 95% CI = 5.39-18.56; GA vs AA: OR = 3.57, 95% CI = 1.84-6.93; dominant model: OR = 8.05, 95% CI = 4.36-14.88; recessive model: OR = 3.83, 95% CI = 2.89-5.08), but not in Caucasians.

Figure 3. Forest plot for meta-analysis of the association between the ACE2 G8790A polymorphism and COVID-19 severity risk.



Publication bias

We conducted Begg's test in order to evaluate publication bias, and no evident publication bias was observed.

Figure 4. Forest plot for meta-analysis of the association between the ACE2 G8790A polymorphism and COVID-19 severity risk in Asians.

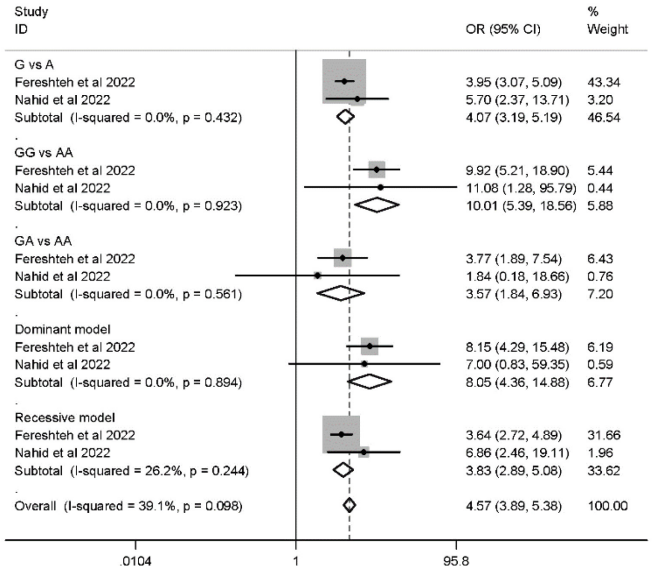


Table 3. Summary of comparative results.

Variables	N	OR (95% CI)				
		G vs A	GG vs AA	GA vs AA	Dominant model	Recessive model
Race						
Asians	2	0.60 (0.08-4.57) R	0.54 (0.02-12.56) R	0.81 (0.33-2.02) F	1.55 (0.11-21.02) R	1.87 (0.24-14.83) R
Caucasians	5	1.30 (0.76-2.23) R	1.60 (0.67-3.85) R	0.48 (0.17-1.36) F	0.60 (0.24-1.46) R	0.89 (0.58-1.35) R
Total	7	0.94 (0.55-1.60) R	0.78 (0.35-1.76) R	0.56 (0.25-1.29) R	0.73 (0.33-1.61) R	1.05 (0.65-1.70) R

Table 4. Summary of different comparative results.

Variables	N	OR (95%CI)				
		G vs A	GG vs AA	GA vs AA	Dominant model	Recessive model
Race						
Asians	2	4.07 (3.19-5.19) F	10.01 (5.39-18.56) F	3.57 (1.84-6.93) F	8.05 (4.36-14.88) F	3.83 (2.89-5.08) F
Caucasians	5	1.13 (0.60-2.10) R	1.07 (0.46-2.53) R	0.83 (0.53-1.30) F	1.02 (0.46-2.24) R	1.16 (0.64-2.11) R
Total	7	1.69 (0.81-3.51) R	2.02 (0.67-6.10) R	1.24 (0.63-2.46) R	1.79 (0.65-4.96) R	1.74 (0.88-3.45) R

N: number; CI: confidence interval; OR: odds ratio; R: random; F: fixed.

Functional predictions

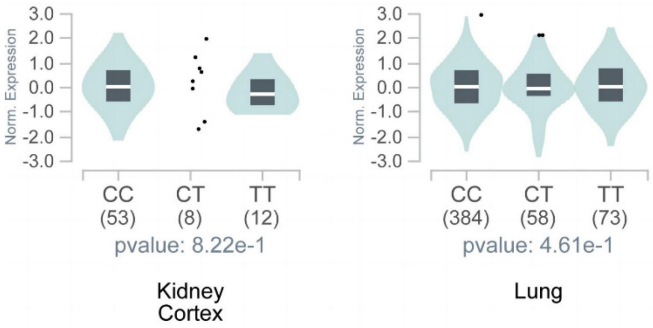
GTEx portal data showed a significant association between the *ACE2* G8790A polymorphism and the gene expression level of *ACE2* in lung and kidney. The G allele of *ACE2* G8790A polymorphism significantly correlated with increased *ACE2* expression (Figure 5). Data collected in HaploReg suggested no linkage disequilibrium of G8790A polymorphism with additional variants of the *ACE2* gene.

Discussion

There is currently a global pandemic of COVID-19. Epidemiological studies indicate that most COVID-19 patients had mild to moderate symptoms and were at risk of severe or life-threatening conditions. As a multifactorial disorder, COVID-19 is still unclear in terms of its pathogenesis. Genetic and environmental factors are both implicated in COVID-19 pathogenesis, and SNPs of certain vulnerable genes may also contribute to the disease's development. Several studies have reported a possible relationship between *ACE2* G8790A polymorphism and COVID-19. COVID-19, however, has not yet been elucidated in detail, primarily due to the limited sample sizes used in single-case-control studies. A systematic evaluation of the impact of the *ACE2* G8790A polymorphism in COVID-19 was performed using electronic databases and relevant literature.

This is the first meta-analysis that summarizes the existing data regarding the relationship between COVID-19 susceptibility and *ACE2* G8790A polymorphism, and included 10 articles. According to our study, the *ACE2* G8790A polymorphism is not associated with COVID-19 risk. Considering additional possible confounding factors, we conducted subgroup analyses as well. Based on subgroup analysis stratified by race, such polymorphism might not be associated with COVID-19 risk in Asians and in Caucasians. Furthermore, we found that this polymorphism was not associated with COVID-19 severity. However, subgroup analysis stratified by race suggested that *ACE2* G8790A polymorphism was related to COVID-19 severity in Asians. Ethnicity has been shown to affect allele frequencies. As a result of the COVID-19 severity data, we found that the frequency of the *ACE2* G allele was significantly higher in Asians (0.48) than in Caucasians (0.34). Clinical manifestations after SARS-CoV-2 infection are directly related to allele differences in G8790A polymorphism. Moreover, sensitivity analysis was also performed, revealing statistical robustness of our findings. No evident publication bias was found.

Figure 5. Violin plot shows the correlation between ACE2 G8790A polymorphism with ACE2 expression. The figure was from the GTEx.



There are several hypotheses put forward to explain the above finding that *ACE2* G8790A polymorphism is associated with COVID-19 severity risk in Asians. According to the analysis of eQTL in GTEx, *ACE2* G8790A polymorphism was directly associated with the increased expression level of *ACE2*. Furthermore, Asselta and colleagues have reported that the substitution of G for A increased the splice site strength by 9.2%, increasing the expression of *ACE2* [21]. COVID-19 patients can develop lung-related complications due to the high expression levels of *ACE2* in the lungs [22]. *ACE2* G allele was also associated with a COVID-19 cytokine storm (C-reactive protein, ferritin, lymphocytes, and neutrophils) and thrombocytopenia caused by platelet aggregation in microthrombi [10]. In addition, individuals in Asian populations possess higher *ACE2* transcript levels than populations of Caucasian and African descent [8]. These findings might explain the causation behind *ACE2* G8790A polymorphism influencing COVID-19 severity.

Previous studies have shown that genetics plays a critical role in the immune response to vaccines. The proportion of genetic factors that induce vaccine responses ranges from 36.0% to 88.5% [22]. There is some effect of gene polymorphisms on vaccine immune response rates. Genetic polymorphisms could lead to the development of new vaccines by understanding their functional and mechanistic effects. An association study between human leukocyte antigens (HLAs) and humoral immunity to influenza vaccinations was conducted by Gelder *et al*. Vaccination with influenza vaccine affects antibody levels in normal responders and non-responders depending on *HLA* gene polymorphisms [23]. The constructive contribution that the G8790A polymorphism of *ACE2* can make to the design of COVID-19 vaccines needs to be explored further. This paper serves as a reminder to medical

decision-makers to include G8790A polymorphism in *ACE2* gene in future COVID-19 vaccine designs.

The present study has some limitations. First, we included only English language studies. Therefore, studies that are published in non-English languages were overlooked. Second, the present work did not adjust OR values for potential factors such as age and gender. Third, our results may also be affected by gene-environment and gene-gene interactions, which cannot be evaluated due to the insufficient data.

Conclusions

There was a clear association between the *ACE2* G allele and severity of COVID-19 in Asians. Further research is needed for the detection of potential gene-environment and gene-gene interactions.

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