

## Letter to the Editor

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# COVID-19 infections are also affected by human ACE1 D/I polymorphism

<https://doi.org/10.1515/cclm-2020-0425>

Received April 2, 2020; accepted April 3, 2020

**Keywords:** angiotensin-converting enzyme; COVID-19; plasma proteins; polymorphism.

To the Editor,

The outbreak of the COVID-19 pandemic shows a marked geographical variation in its prevalence and mortality. As no viral mutations have been reported, which can explain the important geographical variations, the question arises if genetic variation of the host may affect the outcome of COVID-19 infection. We therefore postulated that the variability in genotype distribution of a number of immune-related human plasma proteins showing a marked geographical variation [1–3] might partly explain the variable prevalence of the COVID-19 infection.

Prevalence and mortality data (per 1,000,000 inhabitants) of the COVID-19 infection from a number of European, North-African and Middle East countries were included in the study: Algeria, Austria, Belgium, Bulgaria, Cyprus, Croatia, Czech Republic, Denmark, Egypt, Estonia, Finland, France, Germany, Greece, Hungary, Iran, Israel, Italy, Jordan, Moldova, the Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Saudi Arabia, Sweden, Switzerland, Tunisia, Turkey and the United Kingdom were included in the analysis. Data reported on March 28, 2020 by Johns Hopkins were analyzed [4]. Furthermore, the time interval since the start of the infection in each country was recorded for synchronizing the data.

Concomitantly, data on the geographical variation of a number of immune system-related human plasma protein polymorphisms on the deletion/insertion (D/I)

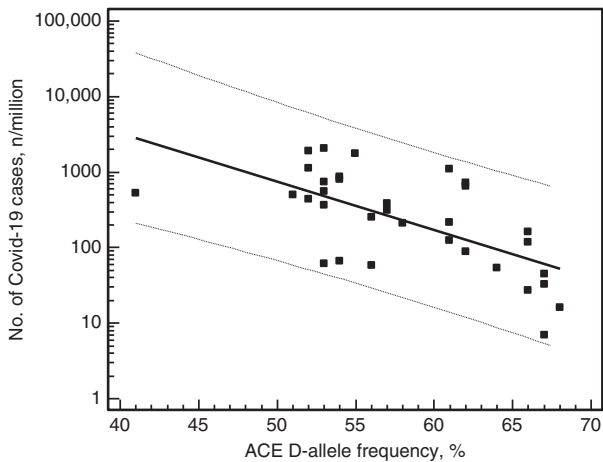
polymorphism of the angiotensin-converting enzyme 1 (*ACE1*) gene [3], human homeostatic iron regulator protein (HFE) [2], complement factor C3 [5], haptoglobin [6] and vitamin D binding protein [7] were collected from the literature.

In the multiple regression analysis model, the prevalence of COVID-19 significantly correlated with ACE1 polymorphism. The other investigated polymorphisms (complement C3 [F and S alleles], HFE [C282Y mutation], haptoglobin [Hp1 and Hp2 alleles] and vitamin D binding protein [DBP1 and DBP 2 alleles]) did not show a significant correlation with COVID-19 prevalence. Figure 1 shows the regression equation. The log-transformed prevalence of COVID-19 in 33 countries (on April 1, 2020) negatively correlated with the ACE D allele frequency:  $\log(\text{prevalence; no. of cases}/10^6 \text{ inhabitants}) = 6.074 - 0.064(\text{D-allele frequency, \%})$ ,  $r^2 = 0.410$ ;  $p = 0.0001$ . The model improved when the onset of the epidemic in each country was taken into account:  $\log(\text{prevalence; number of cases}/10^6 \text{ inhabitants}) = 6.163 - 0.055(\text{D-allele frequency, \%}) - 0.012(\text{days since Jan 1, 2020})$ ,  $r^2 = 0.476$ ;  $p < 0.0001$ . Similarly, COVID-19-associated mortality did only correlate with ACE1:  $\log(\text{mortality; number of cases}/10^6 \text{ inhabitants}) = 4.767 - 0.070(\text{D-allele frequency, \%})$ ,  $r^2 = 0.285$ ;  $p = 0.01$ , and not with any of the other investigated plasma protein polymorphisms. Also, this correlation improved when the onset of the epidemic was taken into account:  $4.955 - 0.055(\text{D-allele frequency, \%}) - 0.026(\text{days since Jan 1, 2020})$ ,  $r^2 = 0.457$ ;  $p < 0.0001$ .

Our findings suggest that the ACE1 D/I polymorphism may be regarded as a confounder in the spread of COVID-19 and the outcome of the infection [8]. The findings are remarkable as all plasma protein polymorphisms investigated show a certain East-West gradient in Europe [6, 7], which is pleading against the bystander role of the ACE D/I polymorphism as a biomarker for historical migrations in the remote past, which passively comigrates with causal genetic factors involved in COVID-19 infection. These findings are in agreement with the role of ACE in lung infections caused by coronaviruses [9]. The strength of the association is further highlighted by the variable policy vs. the COVID-19 threat in the various countries during

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**Figure 1:** Prevalence of COVID-19 in 33 countries (on April 1, 2020) vs. ACE1 D-allele frequency (%):  $\log(\text{prevalence; no. of cases}/10^6 \text{ inhabitants}) = 6.074 - 0.064(\text{D-allele frequency, \%})$ ,  $r^2 = 0.410$ ;  $p = 0.0001$ .

the early phase of the COVID-19 outbreak and the variable onset of the infection in the studied countries. The D/I polymorphism in intron 16 of ACE1 is associated with alterations in circulating and tissue concentrations of ACE. The deletion is associated with a reduced expression of ACE2. Coronaviruses (severe acute respiratory syndrome coronavirus [SARS-CoV] and SARS-CoV-2) are able to bind to their target cells through ACE2 [9, 10]. ACE2 facilitates rapid viral replication, whereas depletion of ACE2 from the cell membrane enhances the damaging effects of Ang II in the lung [8]. As the ACE D/I genotype might be involved in the pathogenesis of COVID-19 infection, further studies are required to assess the clinical outcome of COVID-19 infection in ACE DD, DI and II carriers and to study the exact role of the ACE polymorphism in COVID-19 infection and its therapy response. Including ACE D/I polymorphism into mathematical models describing COVID epidemics could improve model accuracy.

**Author contributions:** All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

**Research funding:** None declared.

**Employment or leadership:** None declared.

**Honorarium:** None declared.

**Competing interests:** Authors state no conflict of interest.

**Informed consent:** Informed consent was obtained from all individuals included in this study.

**Ethical approval:** N/A.

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