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C3 and ACE1 polymorphisms are more important confounders in the spread and outcome of COVID-19 in comparison with ABO polymorphism

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With interest, we read the paper of Dai,[1] regarding the association between ABO blood group and coronavirus disease-19 (COVID-19). The paper suggests that subjects with blood group A, especially those with cardiovascular diseases, in particular hypertension, need to be quarantined and protected from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection or need to be under special medical care to be prevented from deterioration and severe progression.

To verify the role of the A allele in COVID-19, we have collected epidemiological data on several polymorphisms from 54 countries and have compared them with the prevalence and mortality data of SARS-CoV-2 infection in a univariate and multivariate regression model. European, African, Mediterranean, Middle East and Asian countries were included in the present study: all EU countries, Algeria, Belarus, Bosnia & Herzegovina, China, Djibouti, Egypt, Ethiopia, Iceland, India, Iran, Israel, Japan, Jordan, Korea, Moldova, Morocco, Norway, Oman, Russia, Saudi Arabia, Serbia, Switzerland, Tunisia, Taiwan, Turkey and the UK. Data reported on 30 April 2020 by Johns Hopkins were analysed.[2] The time interval since the start of the infection in each country was recorded to synchronize the data. Data on the occurrence of polymorphisms of angiotensin-converting enzyme 1 (*ACE1*), complement component 3 (*C3*), galactoside 2-alpha-L-fucosyltransferase 2 (*FUT2*) were collected from the literature.[3] Only studies with a sufficient sample size (>50 participants) and which were in agreement with the Hardy–Weinberg equilibrium (as a quality check) were used as inclusion criteria in our analysis.

C3 is a central component of the innate immune system.[4] A single base substitution in C3 defines two alleles: slow (S) and fast (F), and three phenotypes (C3 SS, C3 FS and C3 FF). ACE1 is characterized by a deletion/insertion (D/I) polymorphism, which largely determines the ACE expression. ACE1 shows a structural homology with ACE2, the receptor for the SARS-CoV-2 virus. An association between the D-allele of ACE1 and COVID-19 prevalence and mortality has been described.[3] The secretor status (controlled by the *FUT2* or *Se* gene) refers to the presence or absence of ABO blood group antigens in body fluids. People secreting these antigens in their body fluids are referred to as secretors, while people who do not are non-secretors. The secretor status has important consequences for the immune defence: for example, non-secretors have a reduced norovirus susceptibility. Expression of the Lewis blood group antigens is also affected by the secretor status. [5]

In a univariate approach, correlation between COVID-19 prevalence and the A allele was significant: log (prevalence; number of cases/10^6 inhabitants) $= 2.00 + 0.050$ (A allele frequency, %) – 0.008 (date of first case, days since 1 January 2020), $r^2 = 0.122$; $p = 0.04$. Similarly, correlation between the A allele and COVID-19 mortality was significant: log (mortality; number of cases/10^6 inhabitants) $= 0.589 + 0.091$ (A allele frequency, %) – 0.011 (date of first case, days since 1 January 2020), $r^2 = 0.232$; $p = 0.002$. The *FUT2* gene did not show a correlation with COVID-19 prevalence/mortality. The A allele showed a strong correlation with C3 polymorphism (S allele) ($r^2 = 0.451$, $p < 0.001$). In a multivariate regression analysis for predicting COVID-19 prevalence (Table 1), a determination coefficient of 0.372 was calculated for the model. Significance of the A allele got lost, whereas C3 and

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Table 1. Multivariate model for predicting COVID-19 prevalence ($n/10^6$ inhabitants) ($r^2 = 0.372$, $p = 0.0006$).

Parameter	Coefficient	Standard error	t	p-value	VIF
Constant	12.775				
ABO polymorphism (A allele frequency)	–0.028	0.029	–0.947	NS	2.144
C3 S allele frequency	–0.091	0.024	–3.818	0.0004	3.252
ACE D allele frequency	–0.020	0.009	–2.147	0.0378	1.685
Start of pandemic (days since 1 January 2020)	–0.014	0.005	–2.789	0.0080	1.607

ACE: angiotensin-converting enzyme; C3 S: complement component 3 (slow); NS: not significant; VIF: variance inflation factor

Table 2. Multivariate model for predicting COVID-19 mortality ($n/10^6$ inhabitants) ($r^2 = 0.480$, $p < 0.0001$).

Parameter	Coefficient	Standard error	t	p-value	VIF
Constant	16.883				
ABO polymorphism (A allele frequency)	–0.030	0.037	–0.831	NS	2.144
C3 S allele frequency	–0.140	0.030	–4.670	<0.0001	3.252
ACE D allele frequency	–0.022	0.011	–1.912	NS	1,685
Start of pandemic (days since 1 January 2020)	–0.021	0.006	–3.421	0.0014	1.607

ACE: angiotensin-converting enzyme; C3 S: complement component 3 (slow); NS: not significant; VIF: variance inflation factor

ACE1 polymorphisms were determinants for the COVID-19 prevalence. Similarly, only C3 polymorphism was a significant determinant for COVID-19 mortality ($r^2 = 0.480$, $p < 0.0001$) (Table 2).

C3 and ACE1 polymorphisms may be regarded as confounders in the spread and outcome of COVID-19. The C3 polymorphism is a representative of the first principal component of European gene frequencies, whereas the ABO*A allele shows a weak association with the sixth principal component.[2] Although we could confirm an association between the A allele and COVID-19 prevalence/mortality in a univariate analysis, the A allele lost its significance when other polymorphisms (C3, ACE) were integrated into the model. Like the majority of genetic polymorphisms, the ABO blood group polymorphism shows an east to west gradient in Europe,[2] which passively comigrates with causal human genetic factors involved in COVID-19. As the A allele was eliminated as a significant determinant in the multivariate analysis, its role in COVID-19 seems to be secondary. Furthermore, the lack of correlation between COVID-19 prevalence/mortality and the FUT-2 polymorphism pleads against a major role for the A allele in COVID-19.

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