Letter to the Editor – Point

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No significant correlation between ACE Ins/Del genetic polymorphism and COVID-19 infection

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To the Editor,

I read with great interest the study by Delanghe and his colleagues entitled “COVID-19 infections are also affected by human ACE1 D/I polymorphism” that was published in Clinical Chemistry and Laboratory Medicine [1]. Angiotensin-converting enzyme (ACE; MIM: 106180) is involved in the conversion of angiotensin I to angiotensin II [2]. The ACE has numerous genetic variations including functional polymorphism of insertion/deletion (Ins/Del) [3]. The Del allele shows higher ACE activity [4]. The authors reported correlation between the frequency of the Del allele of the ACE Ins/Del polymorphism and prevalence and mortality rates of COVID-19 in 33 countries (25 European, three north-African and five Middle East countries). They found that the log-transformed prevalence of COVID-19 and the log-transformed mortality due to COVID-19 in 33 countries (on April 1, 2020) are negatively correlated with the Del allele frequency [1]. It should be noted that very recently the authors reported similar findings based on statistical analysis in 25 European countries [5].

Although the COVID-19 infection was reported from Wuhan, China (at the end of 2019), it was distributed to other countries after a short time, and at present it is a pandemic infection. The pandemic of COVID-19 shows a geographical pattern in its prevalence and mortality. It is self-evident that several factors are involved in its prevalence, fatality and mortality. Different genotypes of several genetic polymorphisms of certain genes, at least in part, might be accounted for susceptibility to COVID-19 infection.

Each gene pool has its own specific frequencies for alleles, genotypes and combinations of genotypes. In the case of polymorphic linked loci, gene pools reveal much more differences with each other. If the risk of COVID-19 infection is to be associated with some polymorphic loci, then it is expected that populations will show different patterns for epidemiological parameters.

However, I have some comments on the aforementioned study. First, the authors reported negative correlations between the ACE Del allele with the prevalence and mortality of COVID-19 [1, 5]. It should be noted that based on previous studies the Del allelic frequencies in eastern Asian populations, such as in Chinese, Korean, Taiwanese and Japanese, are lower than in European populations [6]. If there is an inverse relationship between the allelic frequency of Del and the prevalence of COVID-19, the prevalence and mortality of the disease in Eastern Asians are expected to be higher than in European populations. Interestingly, the prevalence and mortality of COVID-19 in these countries are extremely low (please see COVID-19 Coronavirus Pandemic data presented at the website: https://www.worldometers.info/coronavirus/#countries), which reveal a strong disagreement with the aforementioned studies [1, 5]. If data of Asian and European countries were used for analysis, it seems that we would observe no correlation between the ACE Ins/Del polymorphism and the prevalence of COVID-19 infection or the mortality due to COVID-19.

Second, the Del allele has a frequency of about 51%–66% among Europeans, whereas the prevalence of COVID-19 infection or COVID-19-associated mortality shows much higher differences between European countries. The authors supposed that about 38% of the variability of the prevalence can be explained by the relative frequency of the Del allele [5]. It should be noted that the study has an ecologic study design and such conclusion is not correct and is an example of ecologic fallacy.

Third, in addition to hereditary factors that can affect the prevalence, fatality and mortality of a disease, various environmental and social factors are also involved. Regarding the COVID-19 infection, we should consider the economic situation and the level of health services

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in different countries. For example, in some countries, laboratory tests were extensively used to identify infected persons, while in some other countries very few tests have been performed. It should be noted that in Algeria, Egypt and Tunisia, 148, 879 and 1596 tests per 10^6 individuals have been performed, respectively, whereas 34059, 33747, 29473 and 26293 tests per 10^6 individuals were performed in Estonia, Cyprus, Portugal and Switzerland, respectively (on April 24, 2020). The reported prevalence (and also mortality) from a country may be affected by the proportion of performed laboratory diagnostic tests, which is highly dependent on the economic power of the country. These two factors (country income and number of tests per 10^6 people) show significant differences between countries and might act as confounding factors in the study of relationship between the Del allelic frequency and the prevalence or mortality of COVID-19. Therefore, these important variables should be included in the statistical model. Taken together, the results presented by Delanghe and his colleagues should be interpreted with caution.

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