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Could angiotensin-converting enzyme 1 *I/D* polymorphism be a modificator of COVID-19 response in different populations, diseases, and/or conditions?

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Dear Editor,

Several articles recently discussed the potential relevance of the insertion/deletion (*I/D*) polymorphism in the angiotensin-converting enzyme 1 (*ACE1*) gene to COVID-19 infection.[1–4] Their data raise the possibility that the *ACE1 D* allele might be a protective factor in the spread and outcome of COVID-19 in various European, North-African, and Middle Eastern populations.[1–3] However, data presented in the meta-analysis investigating the frequency of *ACE1 D* allele distribution in various European countries revealed that the frequency of that allele was the highest in the countries most severely affected by COVID-19 infection, such as Spain, Italy, and UK.[5] Specifically, the frequency of *ACE1 D* allele in Spanish, Italian, and UK general population was estimated at 63%, 58%, and 53%, respectively, while the total number of cases and deaths per million to date were 6328 and 606 for Spain, 3975 and 575 for Italy, and 4584 and 642 for UK.[6] Those data suggest that higher frequency of the *ACE1 D* allele might be rather risk than protective factor in COVID-19 infection. Importantly, higher frequencies of *ACE1 D* allele in general Spanish, Italian, and UK populations are also accompanied by higher frequencies among the elderly individuals, who are at the same time the most vulnerable to COVID-19 infection.[5] In line with this, the relatively low frequency of the *ACE1 D* allele, estimated at 49%, observed in the general Croatian population[5] might explain the rather favorable epidemiological situation in Croatia related to COVID-19 infection. Specifically, since the February 25 outbreak of the COVID-19 pandemic in Croatia, the total number of cases per million to date is 656, while total number of deaths per million is 26, suggesting that Croatia has been rather successful in overcoming COVID-19.[6]

In the past 15 years, our study groups have been investigating the possible relevance of the *ACE1 I/D* polymorphism in various diseases and/or conditions in the Croatian population. Most of our studies suggest that the *ACE1 D* allele as well as the *ACE1 D/D* genotype may be risk factors in multiple sclerosis,[7,8] schizophrenia,[9] and lung cancer.[10] Importantly, we have also found that the risk effects of the *ACE1 D* allele and *ACE1 D/D* genotype were in general more prominent among male patients with multiple sclerosis[7,8] and schizophrenia.[9] Indeed, COVID-19 infection has previously been associated with sex,[11] and a recent article discussing the angiotensin-converting enzyme 2 (encoded by the *ACE2* gene), which has been known to cooperate with *ACE1* in the renin–angiotensin system, hypothesizes that sex differences in COVID-19 severity may be related to the *ACE1* and *ACE2* genes.[4]

The aim of this communication is to emphasize the need for further investigation of the relevance of *ACE1 I/D* polymorphism in COVID-19 infection in different populations. Studies on the potential role of *ACE1 I/D* polymorphism in COVID-19 infection among individuals with different diseases and/or conditions are also warranted. Finally, it would be interesting to address the effect of *ACE1 I/D* polymorphism on COVID-19 infection based on age and sex as a confounders.

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