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SHORT COMMUNICATION

Could the CCR5-Δ32 Mutation be Protective in SARS-CoV-2 Infection?

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Summary

Increasing evidence points to host genetics as a factor in COVID-19 prevalence and outcome. CCR5 is a receptor for proinflammatory chemokines that are involved in host responses, especially to viruses. The CCR5 Δ32 minor allele is an interesting variant, given the role of CCR5 in some viral infections, particularly HIV-1. Recent studies of the impact of CCR5-Δ32 on COVID-19 risk and severity have yielded contradictory results. This ecologic study shows that the CCR5-Δ32 allelic frequency in a European population was significantly negatively correlated with the number of COVID-19 cases (p=0.035) and deaths (p=0.006) during the second pandemic wave. These results suggest that CCR5-Δ32 may be protective against SARS-CoV-2 infection, as it is against HIV infection, and could be predictive of COVID-19 risk and severity. Further studies based on samples from populations of different genetic backgrounds are needed to validate these statistically obtained findings.

Key words

CCR5-Δ32 • CCR5 • COVID-19 • SARS-CoV-2

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Coronavirus disease 2019 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Paces *et al.* 2020). It is acknowledged that several factors affect variable prevalence and severity of COVID-19, including the economic situation and level of health services in different countries, differences in population density and demographic age distribution, comorbidities of the infected patients (hypertension, obesity, diabetes, chronic kidney disease, cancer, smoking status) etc. Considerable inter-individual and inter-population differences in COVID-19 outcome may also depend on host genetic factors. To identify relevant genetic biomarkers of COVID-19 risk, recent studies have explored polymorphisms of several genes that appear to affect SARS-CoV-2 susceptibility or COVID-19 severity.

C-C chemokine receptor type 5 (CCR5) is a chemokine receptor expressed by numerous leukocytes, including macrophages, T cells, and dendritic cells, and has been shown to play an important role in directing leukocytes to the site of inflammation. Therefore, CCR5 is one of the important checkpoints for promoting inflammation in COVID-19 (Esmaeilzadeh and Elahi 2021). The CCR5-Δ32 (rs333) minor allele is an interesting genetic variant, considering the role of CCR5 in some viral infections (Mehlotra 2020). For example, it has been associated with preventing HIV transmission and delaying progression to AIDS. Given the structural similarities between HIV-1 and SARS-CoV-2, anti-AIDS agents have been proposed as a potential inhibitors of SARS-CoV-2 entry into cells (Hubacek *et al.* 2021) and leronlimab-mediated CCR5 blockade has been shown to generate extreme reductions in plasma viremia (Pattersson *et al.* 2020). However, this

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mutation does not always involve an immunological advantage and has been linked to detrimental effects, as in influenza and West Nile virus infection, including increased risk for fatal outcomes. Regarding SARS-CoV-2, it was recently reported that the gene cluster region at 3p21.31 is associated with severe COVID-19 (Severe Covid-19 GWAS Group 2020) and *CCR5* gene is located within this cluster.

To date, two studies have evaluated a population-level correlation between CCR5-Δ32 mutation and COVID-19 prevalence and mortality, yielding contradictory results. Panda *et al.* (2020) explored 107 countries worldwide (data assessed on June 29, 2020) and reported a significant positive correlation between COVID-19 infection rate per million and mortality rate per million with the frequency of CCR5 Δ32 allele, as well as a positive correlation between CCR5-Δ32 allele frequency and COVID-19 mortality rate in an African population. Recently, we compared CCR5-Δ32 mutation frequency in 39 European countries with COVID-19 prevalence and mortality, as calculated on June 1, 2020, and found no association (Starčević Čizmarević *et al.* 2020). Both studies included data from the first COVID-19 wave, when most European countries had implemented restrictions on population movement to slow SARS-CoV-2 transmission and prevent health systems from becoming overwhelmed. At the end of June 2020, the EU re-opened internal borders, as did other European countries.

The relaxation of restrictions has led to an increased number of cases in most European countries because of increases in social contacts. Although lower rates of mortality and hospitalization were observed during the summer, the situation changed dramatically in the autumn, when Europe faced a second wave of cases at the end of September. According to the European Centre for Disease Prevention and Control, Europe experienced a record high number of new coronavirus cases, reaching 71,365 on September 21, 2020 (www.ecdc.europa.eu/en/covid-19). This surge occurred even in some countries that largely avoided the first COVID-19 wave (Czech Republic) or had favorable epidemiological situations (Southeast Europe) during the first COVID-19 wave.

We were interested in whether the association of CCR5-Δ32 with COVID-19 prevalence and mortality in Europe remained unchanged during this second wave. Here, we present a statistical reanalysis of relevant data, performed on February 1, 2021, a year after the World Health Organization declared the outbreak to be a Public Health Emergency of International Concern.

We obtained the prevalence of the CCR5-Δ32 allele in healthy individuals from 39 European countries based on Solloch *et al.* (2017). The analysis included the following countries: Albania, Austria, Belarus, Belgium, Bosnia and Herzegovina, Bulgaria, Croatia, the Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Italy, Latvia, Lithuania, Luxembourg, Malta, Moldova, Montenegro, the Netherlands, North Macedonia, Norway, Poland, Portugal, Romania, Russia, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey, the United Kingdom, and Ukraine. Data for the prevalence (number of cases/10^6 inhabitants), mortality (number of deaths/10^6 inhabitants), number of diagnostic tests per 10^6 people, and time elapsed since the onset of the epidemic (days since January 1, 2020) in each country were obtained from a WorldOMeter website (www.worldometers.info/coronavirus/countries. Assessed February 1, 2021).

We used multiple regression to evaluate the association between COVID-19 prevalence and mortality and CCR5-Δ32 prevalence, controlling for testing intensity and time elapsed since the onset of the epidemic in each country. To more closely approximate normal distributions for linear regression, we log transformed the data.

Figure 1A and B show the correlation between COVID-19 prevalence and mortality and CCR5-Δ32 allele frequency in European populations. The log-prevalence of COVID-19 was significantly negatively associated with CCR5-Δ32 frequency (partial r=-0.347, p=0.035). In addition, the partial coefficient of the CCR5-Δ32 frequency showed a strong negative association with the log-mortality (partial r=-0.444, p=0.006), after adjustment for the log-number of diagnostic tests and log-onset of the epidemic (days) in each country as possible confounders.

Here we found a negative association of the prevalence of the CCR5-Δ32 allele with COVID-19 prevalence and mortality in the second European wave of the pandemic. Our results are reversed compared with the first analysis, which relied on data up to June 2020 and reflected the initial situation of the COVID-19 pandemic during European lockdowns (Starčević Čizmarević *et al.* 2020). This shift suggests that reanalysis is warranted for other host genetic biomarkers investigated during the first wave of the pandemic.

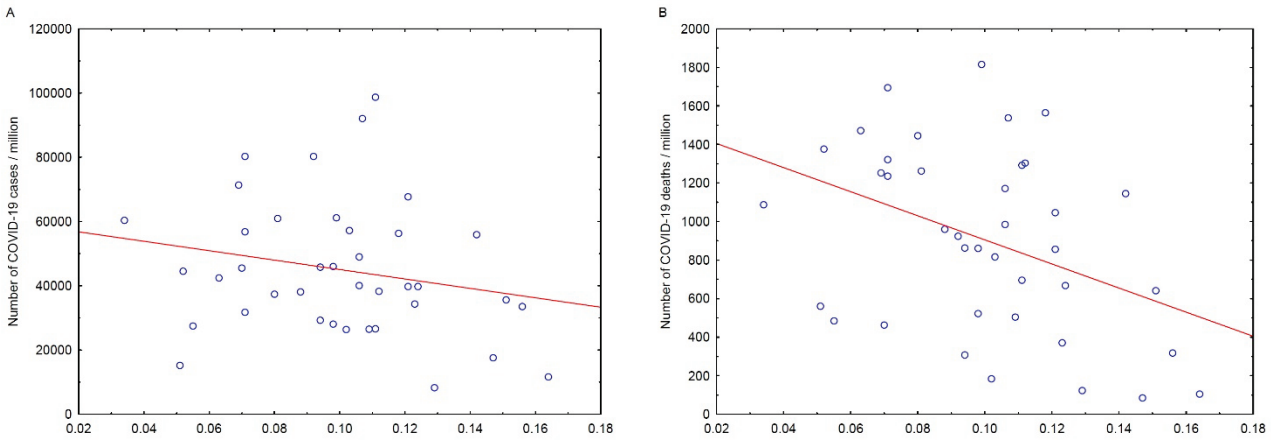

Fig. 1. Correlation between CCR5-Δ32 allele frequency and COVID-19 prevalence and mortality in Europe (on February 1, 2021). (**A**) The number of COVID-19 cases per million inhabitants (r=-0.347, p=0.035). (**B**) The number of COVID-19-related deaths per million inhabitants (r=-0.444, p=0.006).

Our findings in European populations contrast with those of Panda *et al.* (2020), who reported a positive association between the CCR5-Δ32 mutation and global prevalence and mortality. We believe that this earlier study had some relevant limitations. It included 107 countries with populations of varying genetic backgrounds and large differences in type and number of covariates related to COVID-19 risk, including socio-economic status, health care structure, population density, and age distribution. For example, COVID-19 mortality rates in African countries are relatively low compared to those in Europe, likely because of the overall younger age of African populations. On the other hand, Africans living outside their continent of origin are actually at higher risk of COVID-19. Additionally, CCR5 polymorphism distributions are distinct among European, Asian, and African populations. Population surveys have estimated a CCR5-Δ32 allele frequency of approximately 10 % in European populations, but it is absent or rare in Asia and in native populations from Africa, the Americas, and Oceania. In addition, some countries in Panda *et al.*'s (2020) analysis, such as Australia, the United States, Canada, Brazil, and South Africa, are immigrant-friendly nations with highly mixed populations. It is important to include ancestry differences in analytical research and to present separate results for more homogeneous European, Asian, and African populations, as shown by studies on links between other gene polymorphisms and COVID-19 in different parts of the world (Yamamoto *et al.* 2020, Mizokami 2020). Our study was limited to Europe, where populations tend to share a common ancestry and there are no large differences in other risk covariates for COVID-19.

Finally, several factors clearly have affected the variable prevalence and mortality of COVID-19. Although we do not expect multivariate analysis to include all possible variables, Panda *et al.* (2020) did not correct for any potential confounding factors. As an example, the number of laboratory diagnostic tests varies significantly by country and is highly dependent on a nation's economic status. Moreover, the timing of the epidemic outbreak differed by region. For example, in North Africa and the Middle East, the SARS-CoV-2 epidemic was delayed compared to Asia and Europe. These two important variables could have been confounders in Panda *et al.* but were not included their analysis.

In conclusion, we found a significant negative correlation between CCR5-Δ32 allele frequency and COVID-19 case counts and deaths in Europe. The results of this population-level analysis suggest that the CCR5-Δ32 allele may be a predictive biomarker for COVID-19 susceptibility, severity, and mortality. Our findings have certain limitations because of the ecologic study design and should be considered hypothesis generating. However, our results are in agreement with evidence that the CCR5-Δ32 mutation could be a protective factor in patients in the Czech Republic (Hubacek *et al.* 2021), as well as with data suggesting that severe COVID-19 can be treated with CCR5 inhibition (Patterson *et al.* 2020). In contrast, recent study showed that in patients in Germany, the CCR5-Δ32 mutation was not associated with the risk of SARS-CoV-2 infection or with the disease course (Bernas *et al.* 2021). Further studies involving larger populations of asymptomatic, mild, severe, and fatal

COVID-19 cases and with different genetic backgrounds are needed to confirm any impact of CCR5-Δ32 on SARS-CoV-2 infection.

Conflict of Interest

There is no conflict of interest.

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