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CCL5 rs2107538 Variant Is Associated With Protection Against SARS-CoV-2 Infection and Related Mortality: A Population-Based Study

To the Editor—We read with interest Perez-Garcia et al's recent study that looked at the viral load of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the expression of numerous immune genes in the upper respiratory tract of SARS-CoV-2–infected individuals. In 255 subjects investigated, higher viral loads and lower CCL5 levels were linked to intensive care unit (ICU) admission or mortality [1]. However, earlier studies have documented the elevated CCL5 in SARS-CoV-2–infected cases as a predictor of clinical severity [2]. Single-nucleotide polymorphisms in the promoter (rs2107538 and rs2280788) and intronic region (rs2280789) of the *CCL5* gene have been linked to differential *CCL5* expression [3–5]. Given that *CCL5* expression and protein levels have been connected to *CCL5* genetic polymorphisms, we hypothesized that genetic variants in the *CCL5* gene could be associated with the global infection and mortality rate of SARS-CoV-2.

SARS-CoV-2 infection and related death rates per million are available on the worldometer website (https://www.worldometers.info/coronavirus/). Up to now (30 December 2021), about 285 million SARS-CoV-2 infection and 5.4 million deaths have been reported worldwide in 222 countries and territories. We have downloaded various data such as name of the country, infection rate per million, SARS-CoV-2–infected subjects' death rate per million during different random time periods in the year 2021 (14 April, 30 May, 14 June, 22 July, 13 September, 11 October, and 22 December). Genotypes and allele frequencies of *CCL5* polymorphisms (rs2107538, rs2280788, and rs2280789) were obtained from various databases such as 1000 Genome, 8.3 KJPN, Korean population from Korean Reference Genome Database (KRGDB) (https://www.ncbi.nlm.nih.gov/snp/, https://asia.ensembl.org/Homo_sapiens/Info/Index), Genome of Netherlands release 5, and Genetic Variation in Estonian Population. The allele frequencies of *CCL5* polymorphisms were available for 23 countries. Allele or genotypes data were pooled for countries with 2 or more reports in the database (China, 3; Finland, 2; India, 2; Japan, 2; Nigeria, 2; and United States, 4). Details are shown in Supplementary Table 1. Differential frequencies of minor alleles of *CCL5* were noticed worldwide (rs2107538, 12.2% to 47.7%; rs2280788, 1% to 100%; and rs2280789, 0.7% to 30.4%).

Spearman rank correlation analysis was performed to investigate correlation of *CCL5* polymorphisms (rs2107538, rs2280788, and rs2280789) minor alleles with infection and mortality rate per million. As shown in Table 1, the minor allele of rs2107538 polymorphism was negatively correlated with the SARS-CoV-2 infection and mortality rate. Interestingly, the correlation of rs2107538 minor allele remained valid for all time periods (14 April, 30 May, 14 June, 22 July, 13 September, 11 October, and 22 December) considered in the present investigation. However, no significant correlation between the minor allele frequency of the other 2 *CCL5* polymorphisms (rs2280788 and rs2280789) with SARS-CoV-2 infection and mortality rate per million was observed (Table 1). These observations suggest a possible role of the *CCL5* rs2107538 polymorphism in SARS-CoV-2 infection and mortality in the worldwide population.

Association of *CCL5* rs2107538 polymorphism with levels of CCL5 has been documented: the GG genotype subjects had significantly higher concentration of CCL5 protein than the AA genotype [5]. Our current investigation indicated a decreased rate of SARS-CoV-2 infection in a population with a higher prevalence of the *CCL5* rs2107538 minor allele (A). The

Table 1. Correlation of *CCL5* Polymorphisms (rs2107538, rs2280788, and rs2280789) Minor Allele Frequency With SARS-CoV-2 Infection or Death Rate in Different Countries Worldwide

	rs2107538 G > A		rs2280788 C > G		rs2280789 T > C	
Date	Cases/Million	Death/Million	Cases/Million	Death/Million	Cases/Million	Death/Million
14 Apr 2021	**−0.725, <.0001**	**−0.673, .0004**	−0.198, .3411	−0.111, .602	−0.317, .122	−0.166, .437
30 May 2021	**−0.735, <.0001**	**−0.703, .0002**	−0.185, .375	−0.131, .541	−0.289, .160	−0.227, .284
14 Jun 2021	**−0.739, <.0001**	**−0.716, .0001**	−0.184, .377	−0.087, .684	−0.286, .164	−0.225, .288
22 Jul 2021	**−0.738, <.0001**	**−0.728, <.0001**	−0.223, .282	−0.104, .625	−0.310, .130	−0.255, .229
13 Sep 2021	**−0.766, <.0001**	**−0.763, <.0001**	−0.357, .079	−0.145, .486	−0.388, .054	−0.153, .464
11 Oct 2021	**−0.764, <.0001**	**−0.759, <.0001**	−0.39, .054	−0.177, .396	−0.059, .777	−0.088, .682
22 Dec 2021	**−0.760, <.0001**	**−0.755, <.0001**	−0.393, .051	−0.170, .414	−0.3489, .087	−0.169, .417

The correlation between the prevalence of minor alleles and SARS-CoV-2 cases/million or related death/million were analyzed by the Spearman rank test. Spearman rank coefficient value and probability values are given. *P* value less than .05 was taken as significant. Statistically significant values are in bold.

mechanism by which decreased CCL5 levels protect against SARS-CoV-2 infection is unknown. Interestingly, the low production allele (A) of the rs2107538 polymorphism also demonstrated an inverse connection with SARS-CoV-2 infection-related mortality in the studied group. Reduced CCL5 levels have been shown to be protective against SARS-CoV-2 infection-related death in an earlier report [2, 6]. In agreement with earlier observations [2, 6], the study by Perez-Garcia et al [1] also demonstrated a significant association of lower CCL5 with protection against ICU admission or death during hospital admission. However, the SARS-CoV-2 load was linked with the risk of ICU admission and death [1]. Taken together, our current analysis and previous reports indicate that viral load and CCL5 levels should be considered to understand the significance of CCL5 in the pathogenesis and mortality associated with SARS-CoV-2 infection.

Our current study has several weaknesses. First, it included minor allele data from 23 countries. Due to the lack of *CCL5* genotype or allele data in the database for other countries, those were not considered. Second, we conducted an observational correlation analysis to examine the possible link between *CCL5* alleles and SARS-CoV-2 infection or mortality; nevertheless, a case-control study is the most appropriate method for studying genetic predisposition. Third, our study did not assess confounding factors associated with SARS-CoV-2 infections and death in a community, such as age, sex, and health facilities.

Based on the findings of our study, it can be assumed that the minor allele rs2107538 protects people against SARS-CoV-2 infection and death. However, well-designed case-control studies in diverse ethnic groups, considering larger sample numbers, are required to validate our findings.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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Reply to Pati et al

To the Editor—We have read with interest the letter from Pati et al [1] about our recent article [2], and we appreciate the opportunity to clarify some points.

In their letter, Pati et al say that "the study by Pérez-García et al also demonstrated a significant association of lower CCL5 with protection against ICU [intensive care unit] admission or death during hospital admission." However, our results showed just the opposite. We found that low CCL5 expression levels