Granulin rs5848 (C>T) polymorphism is associated with SARS-CoV-2 infection and mortality.

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Dear Editor,

We read with great interest the recent article by Rieder et al. [1] that demonstrated the importance of progranulin in the pathogenesis of severe coronavirus disease-19 (COVID-19). The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infected subjects displayed higher serum progranulin than those without infection[1]. Furthermore, elevated progranulin has been linked with other severe clinical phenotypes of SARS-CoV-2 infection and adverse disease outcomes. During the treatment, a patient who died had about 3.3-fold higher progranulin compared to the mean progranulin levels of SARS-CoV-2 infected cases[1]. A common genetic polymorphism at 3' untranslated region (3'UTR) in the granulin gene (C>T, rs5848) has been reported in different populations and has been associated with altered mRNA and protein levels [2, 3]. An *in silico* and *in vitro* analysis revealed increased binding of miR-659 with the T allele and suppressed progranulin translation compared to those of the C allele [4]. These observations triggered us to investigate the link between granulin rs5848 polymorphism and SARS-CoV-2 infection susceptibility or related mortality in global populations.

COVID-19 infection and related death rate per million data are available on the worldometer website for 221 countries (https://www.worldometers.info/coronavirus/). Various information such as the country's name, SARS-CoV-2 infection rate per million persons, and the death rate per million inhabitants were extracted (the website was browsed on 19th March 2021). The genotype and allele frequencies of granulin rs5848 polymorphism in healthy subjects from different countries were obtained from 1000 genome projects and gnomAD database. Furthermore, published articles were screened through a PubMed search tool for rs5848 polymorphism, and both allele and genotype frequencies in healthy controls were extracted. Reports with deviated Hardy-Weinberg equilibrium genotype frequencies were excluded from the present investigation. Based on the inclusion and exclusion criteria, a

total of nineteen countries (Gambia, Kenya, Nigeria, Colombia, Peru, China, Japan, Vietnam, Finland, United Kingdom, Bangladesh, Pakistan, Belgium, Germany, Italy, Netherland, Poland, Taiwan, USA) comprise of 18560 healthy controls genotype or allele data for rs5848 polymorphism were considered for the present analysis. Details of the publications and source of data acquisition are mentioned in Supplementary Table-1 and Supplementary Table-2. The frequency of the major allele 'C' ranges from 22% (Nigeria) to 88% (Peru)

The Spearman rank correlation analysis revealed a significant positive link between C allele frequency and SARS-CoV-2 infection (r = 0.612, p = 0.005) and mortality rate per million of the population of the country (r = 0.623, p = 0.004), indicating an essential role of rs5848 genetic variant with a predisposition to SARS-CoV-2 infection and mortality in the worldwide population. Elevated progranulin levels have been reported in the serum of infected patients, and subjects who died during treatment of SARS-CoV-2 had more than three fold higher serum progranulin levels compared to infected cases[1]. As depicted earlier, the subject with rs5848-CC genotype is associated with elevated mRNA and progranulin levels[2, 3]. In addition, another independent investigation also revealed the significant binding of miR-659 to the allele T and suppressed the downstream translation process[4]. Subjects with CC genotype or allele 'C' linked with higher progranulin levels and are susceptible to SARS-CoV-2 infection and related mortality; however, the possible mechanism has remained unknown. It has been demonstrated that PGRN hampers the cytotoxicity of the natural killer cell through suppression of NK cell expansion, reduction in the transcription of granzyme B, and diminished NK cell-mediated lysis of target cells [5]. Thus, individuals with elevated progranulin have diminished antiviral phenotypes and are possibly susceptible to SARS-CoV-2 infections and disease severity. Following this presumption, the influenza virus in mice increased granulin mRNA production and was

positively associated with the disease's severity [6]. Furthermore, administration of granulin antibodies provides defense against influenza-induced mortality in mice[7].

There are some shortcomings to the present study, and these must be summarized. First, due to the smaller number of reports on the prevalence of genotype and allele frequency of progranulin (rs5848) polymorphism, an ethnicity investigation was not performed in the current study. Second, a case-control study is ideal for examining the susceptibility to SARS-CoV-2, and associated mortality of the renalase (rs5848) gene polymorphism, rather than the observational association study. Thirdly, the confounding factors of SARS-CoV-2 deaths, such as age, gender, country GDP, health sector expenditure, number of physicians and nurses for a thousand patients, were not taken into account in the present research.

In conclusion, based on the findings of this study and the previous reports, it can be concluded that the C allele of the progranulin rs5848 polymorphism predisposes to SARS-CoV-2 infection susceptibility and mortality. However, larger sample sizes and case-control studies in different ethnic groups are needed to confirm our findings.

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Figure 1. Correlation of major allele 'C' with SARS CoV-2 infection and mortality rate. SARS-CoV-2 infection and mortality rate per million data were obtained from worldometer website (assessed on 19.03.2021). The genotype and allele frequency of rs5848 polymorphism in healthy subjects of different countries were obtained from 1000 genome projects, gnomAD, and PubMed databases. Spearman rank coefficient analysis was performed to investigate the correlation of allele 'C' with SARS-CoV-2 infection/million (A: r = 0.612, p = 0.005, n = 19), the mortality rate per million (B: r = 0.623, p = 0.004, n = 19). A p-value of less than 0.05 was considered as significant.

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Figure 1