

HYPOTHESES

Ethnic differences in alpha-1 antitrypsin deficiency allele frequencies may partially explain national differences in COVID-19 fatality rates

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Abstract

Infection rates, severity, and fatalities due to COVID-19, the pandemic mediated by SARS-CoV-2, vary greatly between countries. With few exceptions, these are lower in East and Southeast Asian and Sub-Saharan African countries compared with other regions. Epidemiological differences may reflect differences in border closures, lockdowns, and social distancing measures taken by each county, and by cultural differences, such as common use of face masks in East and Southeast Asian countries. The plasma serine protease inhibitor alpha-1 antitrypsin was suggested to protect from COVID-19 by inhibiting TMPRSS2, a cell surface serine protease essential for the SARS-CoV-2 cell entry. Here, we present evidence that population differences in alpha-1 antitrypsin deficiency allele frequencies may partially explain national differences in the COVID-19 epidemiology. Our study compared reported national estimates for the major alpha-1 antitrypsin deficiency alleles PiZ and PiS (*SERPINA1* rs28929474 and rs17580, respectively) with the Johns Hopkins University Coronavirus Resource Center dataset. We found a significant positive correlation ($R = .54$, $P = 1.98e-6$) between the combined frequencies of the alpha-1 antitrypsin PiZ and PiS deficiency alleles in 67 countries and their reported COVID-19 mortality rates. Our observations suggest that alpha-1 antitrypsin deficiency alleles may contribute to national differences in COVID-19 infection, severity, and mortality rates. Population-wide screening for carriers of alpha-1 antitrypsin deficiency alleles should be considered for prioritizing individuals for stricter social distancing measures and for receiving a SARS-CoV-2 vaccine once it becomes available.

KEY WORDS

alpha-1 antitrypsin, COVID-19, rs17580, rs28929474, SERPINA1

Abbreviations: AAT, alpha-1 antitrypsin; ANCOVA, analysis of covariance; COPD, chronic obstructive pulmonary diseases; COVID-19, coronavirus disease-2019; HDI, Human Development Index; PiS, alpha-1 antitrypsin deficiency allele S (*SERPINEA1* rs17580); PiZ, alpha-1 antitrypsin deficiency allele Z (*SERPINEA1* rs28929474); SARS, severe acute respiratory syndrome; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; *SERPINA1*, Serpin Family A Member 1 (the gene coding for alpha-1 antitrypsin); TMPRSS2, Transmembrane Serine Protease 2.

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1 | INTRODUCTION

Differences between countries in state-mandated border closures, lockdowns, and social distancing regulations provide obvious reasons for the great variation between countries in COVID-19 infection rates and morbidity. Differences in cultural customs have also been attributed a role. For example, wearing face masks was common in some Asian countries prior to the current pandemic, and this may have contributed to lower COVID-19 infection and fatality rates in these countries.¹ Genetic variations between ethnic groups have also been proposed as a factor that contributes to differences in COVID-19 epidemiology. The relatively low rates of COVID-19 infection and mortality in East and Southeast Asian countries, including Japan, China, South Korea, Thailand, Vietnam, Cambodia, and Malaysia, are notable, and remain little understood.² Relatively low COVID-19 infection and mortality rates are also notable for several Sub-Saharan African countries. While these rates may be due to lower testing for SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2; the virus causing COVID-19), and fewer international arrivals, they may also reflect genetic variations between the populations. However, at the time of this writing, no studies have reported associations of genetic variations between populations with COVID-19 infection and fatality rates.

The serine protease TMPRSS2 is well established as essential for priming SARS-CoV-2 cell entry, following binding to its ACE2 cell membrane receptor.³ Accordingly, the synthetic serine protease inhibitors nafamostat mesylate and camostat mesylate were shown to inhibit TMPRSS2⁴ and are undergoing clinical trials in COVID-19 patients. The major human blood serine protease inhibitor (serpin) is alpha-1 antitrypsin, which is encoded by the *SERPINA1* gene and produced primarily in the liver, similar to many blood proteins. Comparing regions in Italy, differential alpha-1 antitrypsin genetic deficiency rates were proposed to correlate with COVID-19 infection. This was based on higher rates of both alpha-1 antitrypsin deficiency (carriers of *SERPINA1* rs28929474, termed PiZ) and COVID-19 infection rates in Lombardy, Italy than in central and southern Italian regions.⁵ Based on these observations, as well as on its antiviral and anti-inflammatory properties, alpha-1-antitrypsin was proposed as a tentative host protective factor against COVID-19.⁶ We therefore examined a possible association between the distributions of common *SERPINA1* single nucleotide polymorphisms (SNPs) underlying alpha-1 antitrypsin deficiency and between COVID-19 epidemiology on a global scale.

2 | METHODS

National allele frequency estimates for the alpha-1 antitrypsin PiS (*SERPINA1* rs17580) and PiZ (*SERPINA1* rs28929474)

alleles were obtained from Blanco et al.⁷ National parameters were obtained from the United Nations database and The World Bank Open Data (data.worldbank.org). For combining the effects of the PiS and PiZ alleles on alpha-1 antitrypsin serum concentration, their frequencies were summed, and weighted by their approximate effect size (50% and 90% respectively, according to Mitchell et al.⁸). Confounder correction and assessment of individual factor effect sizes were done using analysis of covariance (ANCOVA). All statistical analyses were made in the R programming environment. Country-specific epidemiological parameters of the ongoing COVID-19 pandemic were compared between all countries using data from the Johns Hopkins University Coronavirus Resource Center⁹ (accessed September 7, 2020). We focused on countries with a population of over one million in order to reduce noise, for example, from small island nations.

3 | RESULTS

We examined if population variations in human serine protease inhibitor (serpin) genes may help explain the lower COVID-19 infection rates and fatalities in East and Southeast Asia and Sub-Saharan Africa, compared to other regions. Among the 43 human serpin genes, *SERPINA1*, coding for alpha-1 antitrypsin, a major blood serine protease inhibitor, showed the most striking variations in SNP frequencies between Europeans and non-Europeans. We examined in particular variations in *SERPINA1* rs28929474 (the PiZ allele). This allele is recognized as the major allele responsible for antitrypsin deficiency in humans, and was recently suggested to account for the higher COVID-19 infection rates in Lombardy compared with other Italian regions.⁵ *SERPINA1* rs28929474 was about eight-fold less frequent in East and Southeast Asian than in South European populations (17 compared to 2 alleles per 1000 individuals). For the milder deficiency PiS allele, *SERPINA1* rs17580 disparity was even greater (86 compared to 5 alleles per 1000 individuals, over a 17-fold reduction). The combined analysis of the global PiZ and PiS allele frequencies is shown in Figure 1A.

Our comparison of epidemiological data showed that nearly all the countries reporting >100 COVID-19 mortalities per million population (as of September 7, 2020) were in Europe or the Americas. In contrast, East and Southeast Asian, and also Sub-Saharan African countries, were the predominant countries with low mortality rates per million population (Figure 1B; Tables S2 and S3). The COVID-19 population-adjusted fatality rates for Thailand, Vietnam, and Cambodia were 0.8, 0.2, and <0.1 per million, respectively⁹; low COVID-19 fatality rates were also notable for several Sub-Saharan African nations, such as Congo, and Mozambique (2 and 0.7 per million, respectively). Thus, the difference is up to ~100-fold lower compared with some European and American countries. The far lower population-adjusted burden

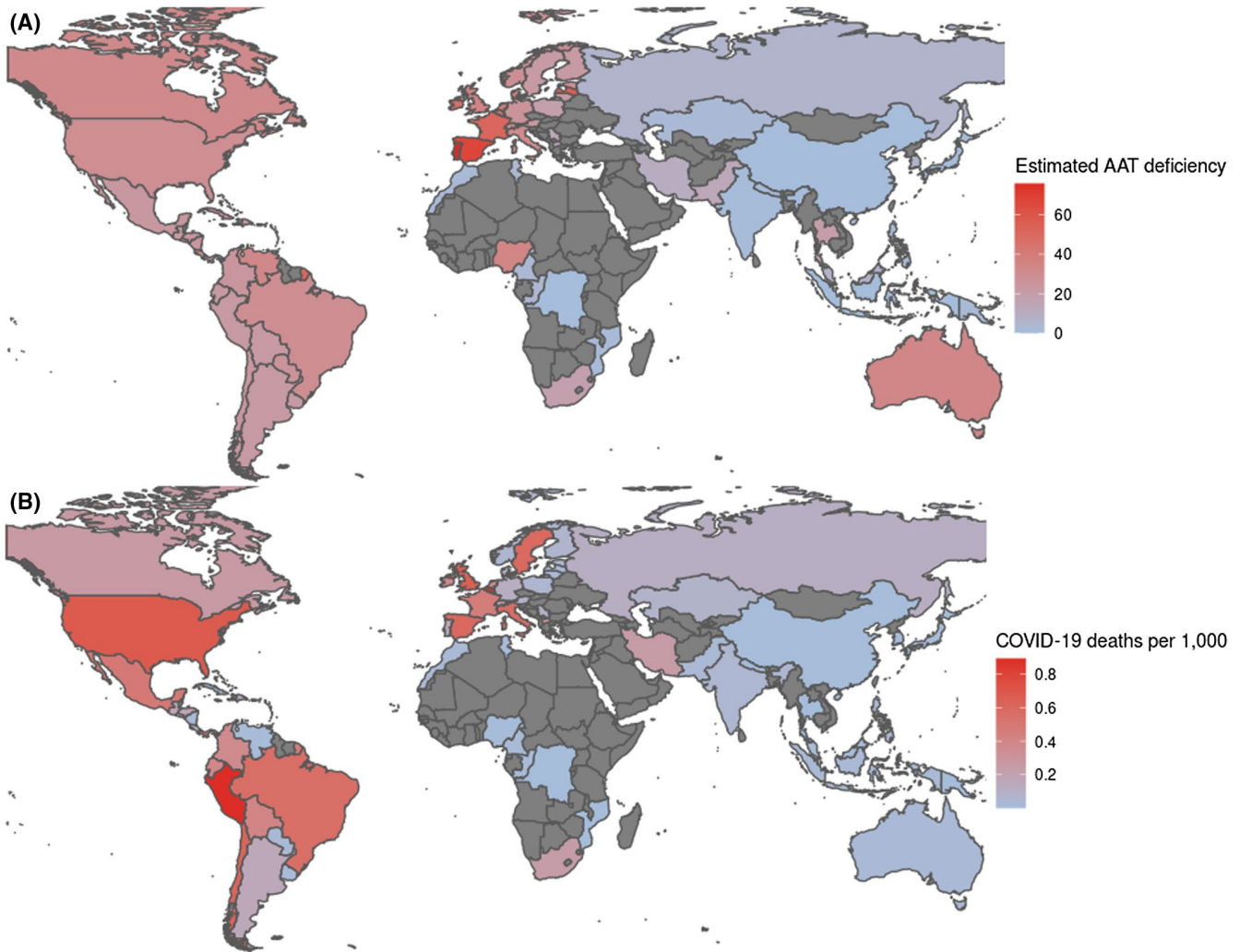


FIGURE 1 Demographics of national alpha-1 antitrypsin (AAT) deficiency and COVID-19 fatality rates per 1,000 population. A, Estimated population-wide alpha-1 antitrypsin (AAT) deficiency, based on frequencies of alleles PiZ and PiS (*SERPINA1* rs28929474 and rs17580, respectively) aggregated by Blanco et al,⁷ and summed proportionally to their respective effect sizes on alpha-1 antitrypsin serum concentration. B, COVID-19 fatality rates per 1,000 population, from the Johns Hopkins University Coronavirus Resource Center⁹ (September 7, 2020)

of COVID-19 in many Asian and Sub-Saharan African countries remains notable when comparing total infections per one million people (Tables S2 and S3).

Lower COVID-19 infection and fatality rates in many Asian and Sub-Saharan countries could stem from confounding factors, such as Human Development Index (HDI), urbanization level, and volume of international travel, as well as lower proportions of elderly people. However, our analysis of covariance resulted in a significant association between estimated alpha-1 antitrypsin deficiency and COVID-19 mortality after controlling for confounders (Figures S1, S2, and Table S1; a full analysis workflow is available at: https://gitlab.com/shep/serpina1_covid_supplementary). Moreover, infection and fatality rates remain among the highest globally in several South-American countries with low HDI and relatively low proportions of elderly persons. The striking difference in the COVID-19 burden between South-American countries and between East and Southeast Asian countries, therefore, seems to

be best explained by ethnic genetic variation. Until additional candidate alleles are found to better explain such national differences, the population variations in the allele frequencies of alpha-1 antitrypsin deficiency present a possible genetic explanation for the varying national COVID-19 burden.

We applied estimated country-specific frequencies of alpha-1 antitrypsin deficiency⁸ to analyze COVID-19 fatalities per thousand inhabitants vs. estimated alpha-1 antitrypsin deficiency in 67 countries (Figure 2). The Pearson correlation of $R = .54$ ($P = 1.98e-6$) suggests an association of alpha-1 antitrypsin deficiency with COVID-19 fatalities. To eliminate the confounding effects of such factors as urbanization and age distribution, we used a one-way analysis of covariance, resulting in significant association also after adjusting for confounders (Figures S1, S2, and Table S1). Considering the above, we propose that the low carrier frequency of alpha-1 antitrypsin deficiency PiZ and PiS alleles in East and Southeast Asian and Sub-Saharan African

vitro inhibition of human TMPRSS2 by alpha-1 antitrypsin, thus suggesting that it might be effective as a COVID-19 treatment.¹⁹

Another recent preprint showed that alpha-1 antitrypsin may inhibit in vitro SARS-CoV-2 infection in human airway epithelium at physiological concentrations.²⁰ A clinical trial of inhaled alpha-1 antitrypsin in COVID-19 patients is currently recruiting participants (NCT04385836). If alpha-1 antitrypsin deficiency will be established as a genetic risk factor for severe COVID-19, and keeping in mind that vaccine availability would be scarce for at least one year following its approval,²¹ population-wide screening for alpha-1 antitrypsin deficient individuals would be desirable for identifying deficient individuals and prioritizing them for vaccination.

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CONFLICT OF INTEREST

The authors declare that no conflicts of interest exist.

AUTHOR CONTRIBUTIONS

D. Gurwitz and N. Shomron conceived the study; G. Shapira analyzed the data and statistics and prepared the figures and Supporting Informations. All authors took part in writing the article.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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