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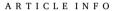
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Original Research

SARS-CoV-2 infection in alpha1-antitrypsin deficiency

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A R T I C L E   I N F O

A B S T R A C T

Alpha1-antitrypsin deficiency arises due to mutations in alpha1-antitrypsin (AAT) gene and represents the most prominent genetic predisposition to chronic obstructive pulmonary disease and emphysema. Since AAT plays important immunomodulatory and tissue-protective roles and since it was suggested to protect from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, we assessed this association in United Kingdom Biobank, a community-based cohort with >500,000 participants. The most common, mild AATD genotypes were associated neither with increased SARS-CoV-2 infection rates nor with increased SARS-CoV-2 fatalities, while the numbers of severe AATD cases were too low to allow definitive conclusions.

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic is a leading cause of death in many countries and because of that, it is of utmost importance to identify subjects susceptible to a life-threatening SARS-CoV-2 infection in order to protect them and to prioritize them in vaccination programs. Several lines of evidence suggest that individuals with alpha1-antitrypsin deficiency (AATD) may constitute such a population [1–3]. AATD arises due to mutations in alpha1-antitrypsin (AAT) gene and represents the most prominent genetic predisposition to chronic obstructive pulmonary disease and emphysema [4,5]. Notably, AAT is the most abundant protease inhibitor in serum and as such plays important immunomodulatory and tissue-protective roles. AAT was suggested to protect from SARS-CoV-2 infection by inhibiting TMPRSS2 [2], a protease facilitating the entry of SARS-CoV-2 into the host cell [6]. In line with that, a positive association between a frequency of AATD mutations and an incidence of SARS-CoV-2 infection as well as SARS-CoV-2-related mortality have been described [3].

To study the association between AATD and SARS-CoV-2 infection, we turned to UK Biobank (UKB), a community-based cohort that recruited >500,000 participants at 22 UK centers. All participants underwent a genotyping with the Affymetrix UK BiLEVE or Affymetrix UK Biobank Axiom® array that contains information about the most clinically relevant AAT variants Pi*Z (rs28929474) and Pi*S (rs17580). The genotyping was available in 487,503 subjects.

As expected, the homozygous Pi*Z genotype (termed Pi*ZZ) that is the predominant cause of severe AAT deficiency (AATD) was relatively

rare (1:3460), while a heterozygous Pi*Z carriage (i.e. Pi*MZ genotype) that results in mild AATD was common (1:28). A combined presence of Pi*S and Pi*Z variants (i.e. Pi*SZ genotype) was seen in 1:560 of participants. Data of COVID-19 tests were extracted on 18th of February 2021 and comprised 113 882 tests that were performed in 60 446 participants. 14 877 subjects were tested positive at least once.

Death notifications including primary ICD10 diagnosis that led to death were obtained through linkage to national death registries. Notably, individuals without Pi*Z/Pi*S variant (termed non-carriers) and subjects with the analyzed AATD genotypes displayed similar rates of SARS-CoV-2 infection ranging between 2 and 3%. However, the usefulness of data on Pi*ZZ subjects is limited by their low numbers (Table 1). Moreover, Pi*MZ and Pi*MS individuals display a similar SARS-CoV-2-related mortality as non-carriers, while the numbers of fatalities in Pi*SZ/Pi*ZZ/Pi*SS individuals are too low to allow meaningful conclusion. These data provide relief to subjects with mild AATD since they do not seem to carry an increased risk of SARS-CoV-2-related injury. This finding is in line with their overall risk for lung-related mortality that is not substantially elevated [4]. On the other hand, individuals with severe AATD should remain cautious given that the current data are scarce and a small study from Portugal suggested an increased risk [1].

This is particularly true when suffering from a clinically relevant lung disease since it constitutes an established risk factor for SARS-CoV-2-related mortality [7]. In conclusion our study does not suggest any increased risk of SARS-CoV-2 infection or death associated with AATD,

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Table 1
Percentage of SARS-CoV-2 positive participants and deaths caused by this infection distributed by alpha1-antitrypsin genotype.

Genotype	n	Tested positive (n)	Tested positive (%)	Death by COVID 19 (n)	Death by COVID-19 (%)
Non-carrier	426 994	12 723	3.0	353	0.08
MZ	17 179	460	2.7	14	0.08
ZZ	141	3	2.1	0	0.00
SZ	875	23	2.6	1	0.11
MS	41 296	1156	2.8	37	0.09
SS	1018	28	2.8	1	0.10

but additional prospective studies are needed for severe AATD before definitive conclusions can be made. Ongoing studies, that are exploring the usefulness of AAT augmentation for treatment of SARS-CoV-2 infection, will shed further light on the importance of AAT in this setting [8,9].

CRediT authorship contribution statement

Carolin V. Schneider: Conceptualization, Methodology, Formal analysis, Data curation, Writing – original draft, Writing – review & editing, Visualization. **Pavel Strnad:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing, Visualization, Supervision, Resources.

Declaration of competing interest

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