

**Geographical Overlap Between Alpha-1 Antitrypsin Deficiency and COVID-19 Infection in Italy: Casual or Causal?**



**Superposición geográfica entre la deficiencia de alfa-1 antitripsina y la infección por COVID-19 en Italia: casual o causal?**

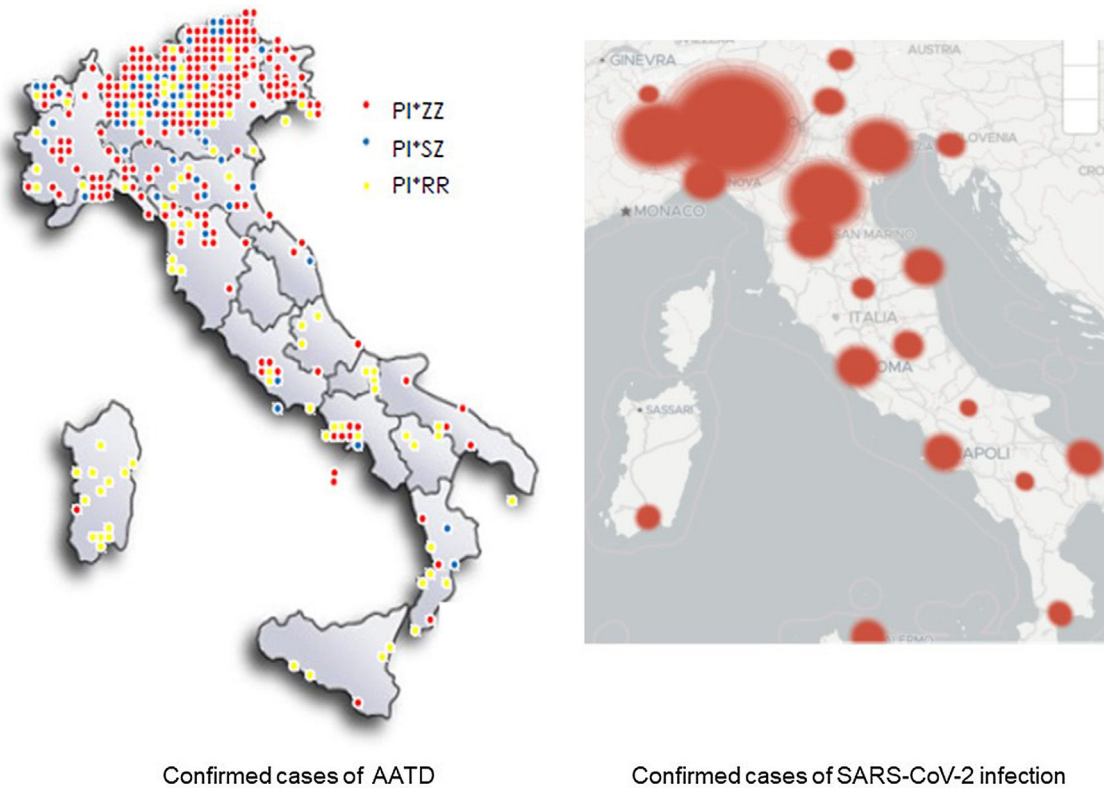
Dear Editor:

At the time when WHO reports that Italy is currently the fifth country in the world for number of cases of Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) infection (225,886 confirmed positive cases to 19<sup>th</sup> May 2020), and the third country for number of related deaths (32,007 fatal cases),<sup>1</sup> it is important to underline that the distribution of affected subjects in our country is very inhomogeneous. 85% of total fatal cases have been registered, in fact, in the Northern Italy (in particular 37.8% in the Lombardia region), with an abrupt decrease from north to south<sup>2</sup> (Fig. 1). This geographic difference is still difficult to understand and many factors may account for it.

$\alpha$ 1-Antitrypsin (AAT) is a serine protease inhibitor whose primary function is to counterbalance the proteolytic action of human neutrophil elastase in the lungs. An autosomal codominant disorder, AAT deficiency (AATD) is characterized by reduced serum level or abnormal function of AAT, that increases the risk of developing

a variety of diseases, including pulmonary emphysema and liver cirrhosis. The most common hereditary disorder in adults, AATD was found to have the highest prevalence rates in northern regions of Italy and to decrease very fast from north to south.<sup>3</sup> Recent data from the Italian Registry for AATD, showed a geographic distribution of confirmed cases very similar to the one reported for SARS-CoV-2 infection, with 47% of the total amount registered in the Lombardia region (237 out of 508)<sup>4</sup> (Fig. 1). Although population size is much smaller than the SARS-CoV-2 patient population, it is noteworthy that AATD is largely under-recognized in our country, with a relation between diagnosed and expected cases of 1-460.<sup>3</sup>

Cell entry of coronaviruses depends on binding of the viral spike (S) proteins to cellular receptors and on S protein priming by host cell proteases. A recent study demonstrated that SARS-CoV-2 uses the SARS-CoV receptor ACE2 for entry and the serine protease TMPRSS2 for S protein priming.<sup>5</sup> Moreover, the Authors reported that a TMPRSS2 inhibitor approved for clinical use blocked viral entry. Based on these results, we argue that a protease-antiprotease imbalance could play a central role in the pathogenicity and virulence of SARS-CoV-2 and we hypothesize that the high prevalence of AATD could have contributed to the devastating impact of coronavirus infection in the Northern Italy. Could causality and not casualness explain geographical overlap between AATD and COVID-19 infection in our country? A detailed analysis of data from the Italian Registry will give us an answer.



**Fig. 1.** Distribution of confirmed cases of Alpha-1 antitrypsin deficiency and Severe Acute Respiratory Syndrome Coronavirus-2 infection in Italy to 18th April 2020 (AATD = alpha-1 antitrypsin deficiency; SARS-CoV-2 = Severe Acute Respiratory Syndrome Coronavirus-2).

**Funding**

This work was not funded by any organization.

**Conflict of interest**

None declared.

**Bibliografía**

1. World Health Organization. Coronavirus disease 2019 (COVID-19) situation report – 120; 2020.
2. Italian Government – Civil Protection Department. Available from: [www.protezionecivile.gov.it](http://www.protezionecivile.gov.it) [accessed 19.05.20].
3. De Serres FJ, Blanco I, Fernandez-Bustillo E. Genetic epidemiology of alpha-1 antitrypsin in southern Europe: France, Italy, Portugal and Spain. *Clin Genet.* 2003;63:490–509.
4. Italian registry of patients with alpha-1 antitrypsin deficiency. Available at: <http://alfa1antitripsina.it/it>.
5. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell.* 2020;181:271–80.

Andrea Vianello\*, Fausto Braccioni

*Respiratory Pathophysiology Division, Department of Cardio-Thoracic and Vascular Sciences, University of Padova, Padova, Italy*

\* Corresponding author.

E-mail address: [andrea.vianello@aopd.veneto.it](mailto:andrea.vianello@aopd.veneto.it) (A. Vianello).

<https://doi.org/10.1016/j.arbres.2020.05.015>

0300-2896/ © 2020 SEPAR. Published by Elsevier España, S.L.U. All rights reserved.