LETTER TO THE EDITOR

**PI*ZQ0**<sub>Attikon</sub> genotype discovery in severe alpha-1 antitrypsin deficiency

A1-antitrypsin (AAT), the major protease inhibitor in serum and severe AAT deficiency (AATD) worldwide, relates mainly to the homozygous state of the PI*Z variant. However, the genetic repertoire of severe AATD is constantly expanding far beyond the homozygous PI*Z variant to a multitude of rare alleles decoding for deficient, dysfunctional or non-null (null-alleles) producing AAT. In recent years a geographical trend towards South Europe also began to appear regarding severe AATD related to rare variants. Recently, we described that by genotyping AATD in Greece, a multiplicity of rare and ultra-rare variants and a diversity of rare combinations were observed in two-thirds of patients, confirming an established North-South European geographical trend in rare variants. The Greek rare variants embraced the null PI*QO<sub>Attikon</sub>, PI*QO<sub>Amersfoort</sub>, PI*QO<sub>Grassite Falco</sub>, PI*QO<sub>Saint-Etienne</sub>, PI*QO<sub>Mattawa</sub> and the deficient variants PI*M<sub>Veereen</sub>, PI*M<sub>Prochida</sub>, PI*M<sub>Malton</sub>, PI*M<sub>Wurzburg</sub> and PI*M<sub>Malton</sub> (null-alleles) producing AAT.

In recent years, the identification of rare and ultra-rare variants in severe AATD related to rare variants is constantly expanding far beyond the homozygous PI*Z variant to a multitude of rare alleles decoding for deficient, dysfunctional or non-null (null-alleles) producing AAT. In recent years a geographical trend towards South Europe also began to appear regarding severe AATD related to rare variants. Recently, we described that by genotyping AATD in Greece, a multiplicity of rare and ultra-rare variants and a diversity of rare combinations were observed in two-thirds of patients, confirming an established North-South European geographical trend in rare variants. The Greek rare variants embraced the null PI*QO<sub>Attikon</sub>, PI*QO<sub>Amersfoort</sub>, PI*QO<sub>Grassite Falco</sub>, PI*QO<sub>Saint-Etienne</sub>, PI*QO<sub>Mattawa</sub> and the deficient variants PI*M<sub>Veereen</sub>, PI*M<sub>Prochida</sub>, PI*M<sub>Malton</sub>, PI*M<sub>Wurzburg</sub> and PI*M<sub>Malton</sub> (null-alleles) producing AAT.

The new variant was named by the University-Clinic and Hospital of discovery PI*QO<sub>Attikon</sub>. In this case the new variant proved clearly pathogenic and seriously deleterious. In the absence of functional studies, this was demonstrated mostly from a high REVEAL score of 0.759 (range 0–1) in association with the clinical presentation of the patient, a never smoker. We have shown that in Greece the majority of patients with severe AATD relates to rare variants instead of the PI*ZZ phenotype that prevails worldwide. Therefore, the discovery of a novel, never reported and clearly pathogenic variant constitutes the epiphenomena of rarities in severe AATD in Greece.

Rare variants are increasingly reported in recent years, by genotyping, mainly in South Europe and surprisingly as reported by us in Greece, the epicenter of rarities in severe AATD. A significant proportion were homozygous QO variants in a multiplicity of different genotype combinations with very low AAT levels, almost imperceptible in fact. Another significant proportion of variants were in compound

---

https://doi.org/10.1016/j.jul.2023.05.003
2531-0437/© 2023 Sociedade Portuguesa de Pneumologia. Published by Elsevier España, S.L.U. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
heterozygous state with the Z variant as in the case described herein and another significant proportion were Mdeficient variants in different combinations with null (Q0) or Z variants not always identifiable without genotyping. From the above observation concern may arise regarding the dose-effectiveness of current dose recommendation of augmentation treatment in zero or almost zero carrying AAT levels, since previous international protocols included exclusively ZZ homozygous phenotypes. Furthermore, additional investigation is necessary regarding the clinical history and fate of these patients as well as the clinical phenotype expressed from carriers of rare variants; a project that fulfills the European Alpha-1 Research Collaboration (EARCO) consortium.

In conclusion, the characterization of a new null variant of SERPINA1 named by the University-Clinic and Hospital of discovery Pi*Q0_Attikon associated with a Pi*Z variant, leading to severe AATD is described. This rare mutation c.1A>G has

Fig. 1 a. High-resolution chest computed tomography of the proband. Normal lung parenchyma distortion due to emphysema. Frontal, sagittal and axial views (from left to right), b: Color-coded visual map on lung density analysis to assess lung emphysema. Red-colored pixels represent attenuation lower than <−950HU, c: Lung density distribution graph. PD15 = -983HU shows an estimated pulmonary density of 17 g/L (for both lungs). The percentage of emphysema (areas of low-attenuation) was estimated ~ 44.2% for both lungs.
never been identified before. Gene sequencing was necessary for genetic diagnosis. In the future the detection of rare genotypes by widening AATD spectrum and geographic distribution of variants may add to understanding of the anthropologic evolution of its mutations and probably help to personalize preventive and therapeutic measures.

Author's contributions

SAP made a major contribution to the concept and design of the study, to the acquisition, analysis and interpretation of data, and wrote the final version of the manuscript with EDM; MV performed the genetic analysis of the patient, made a major contribution to the interpretation of data regarding the new variant and wrote part of the manuscript; AL had major role in the clinical management of the patient, the acquisition and interpretation of data for all family members and critically revised this work for important intellectual content; MB, CL, MD, MFO made major contributions to the interpretation of data for the new variant and revised this work critically for very important intellectual content; EE, LO performed the NGS for the identification of the new variant, provided the figure for Sanger analysis and revised this work critically for important intellectual content; MK, VA had a major role in the management of the patient upon hospitalization and revised this work critically for important intellectual content; SP, CK prepared the radiology figures and figure legends of the manuscript and revised this work critically for important intellectual content; CVF and TG had major contribution in the genetic analysis of the patient in their expert laboratory, played a major role in the interpretation of all data and revised this work critically for very important intellectual content; EDM made a major contribution to the concept and design of the study, to the acquisition, analysis and interpretation of data, had access to all data, supervised the accuracy and integrity of all parts of the work and wrote the final version of the manuscript with SAP. All authors read and approved the final version of the submitted publication.

Declaration of Competing Interest

EE and LO are working at the Progenika Biopharma, a Grifols Company, Derio, Vizcaya, Spain. All authors have provided
an ICMJE statement regarding any other conflict of interest related and un-related to this work.

Financial support
Grifols supported the genetic analysis of the patient

Acknowledgements
The authors acknowledge the contribution of Dr Vasiliki Bizimi, radiologist at the 2nd Department of Radiology, General University Hospital “Attikon”, Medical School, National and Kapodistrian University of Athens, Greece for performing the liver ultrasound and elastography and wish to thank her very much.

References
8. S.A. Papiris a, M. Veith b, 1, A. Lazaratou a, M. Balduyck c, C. Lombard d, M. Dechomet e, M.-F. Odou f, E. Entrena a, L. Osaba a, M. Kallieri b, V. Apollonatou a, S. Prountzos b, C. Kontopoulou b, L. Kolilekas a, I. Ferrarotti b, J.-F. Mornex a, C.-F. Vogelmeier h, 1, T. Greulich b, 1, E.D. Manali h, a–1
9. 2nd Pulmonary Medicine Department, General University Hospital “Attikon”, Medical School, National and Kapodistrian University of Athens, Greece
10. Department of Medicine, Pulmonary and Critical Care Medicine, UKGM, Member of the German Center for Lung Research (DZL), Marburg, Germany
11. CHU de Lille, laboratoire de biochimie et biologie moléculaire (HMNO), centre de biologie pathologie, Faculté de pharmacie et EA 7364 RADEME, laboratoire de biochimie et biologie moléculaire, Université de Lille, Lille, France
12. Laboratoire d’Immunologie, Centre Hospitalier Lyon-Sud, Hospices Civils de Lyon & Université Claude Bernard-Lyon 1, Lyon, France
13. CHU Lille, Service de Biochimie et Biologie moléculaire ‘Héronologie, Métabolisme-Nutrition, Oncologie’, Univ. Lille, Inserm, U1286 – Infinite, F-59000 Lille, France
14. Progenika Biopharma, a Grifols Company, Derio, Vizcaya, Spain
15. 2nd Department of Radiology, General University Hospital “Attikon”, Medical School, National and Kapodistrian University of Athens, Greece
16. 7thPulmonary Department, Athens Chest Hospital “Sotiria”, Athens Greece
17. Center for Diagnosis of Inherited Alpha1-antitrypsin Deficiency, Department of Internal Medicine and Therapeutics, Pneumonology Unit, Fondazione IRCCS Policlinico San Matteo, Università di Pavia, Pavia, Italy
18. Service de pneumologie, Centre national coordinateur de référence des maladies pulmonaires rares, Hôpital Louis Pradel, Hospices Civils de Lyon, Université de Lyon, Université Claude Bernard Lyon 1, UMR754 INRA, IVPC, Lyon, France

* Corresponding author at: 2nd Pulmonary Medicine Department, General University Hospital “Attikon”, Medical School, National and Kapodistrian University of Athens, Greece 1 Rimini Street, 12462 Haidari, Greece.
E-mail address: fmanali@otenet.gr (E.D. Manali).
Received 17 March 2023; Accepted 3 May 2023
Available online 30 May 2023

1 These authors have contributed equally to this work