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SPLF Société de Pneumologie de Langue Française

AP-HP. Université Paris-Saclay

Ospedale San Giuseppe MultiMedica SpA

Sistema Sanitario Regione Lombardia

Milan, Italy
March 3–4, 2023

10th

International Meeting on
PULMONARY RARE DISEASES
AND ORPHAN DRUGS

14.00 **ORAL PRESENTATION SESSION**
Chairs: *Elena Bargagli (Siena, Italy), Olivier Sitbon (Paris, France)*

• Disclosures

I have the following relationship with Pharma Companies:

- **Advisory Boards: Boehringer-Ingelheim**
- **Funding (Grants/Honoraria): Boehringer-Ingelheim, Hoffman-La Roche, CSL Behring, ELPEN Hellas**
- **Research/Clinical Trials: SAVARA, Boehringer-Ingelheim, Hoffman-La Roche**
- **Grifols supported the genetic analysis of the patient**

PI*ZQ0$_{Attikon}$ genotype debut in alpha-1 antitrypsin deficiency

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ORIGINAL ARTICLE

Alpha1-antitrypsin deficiency in Greece: Focus on rare variants

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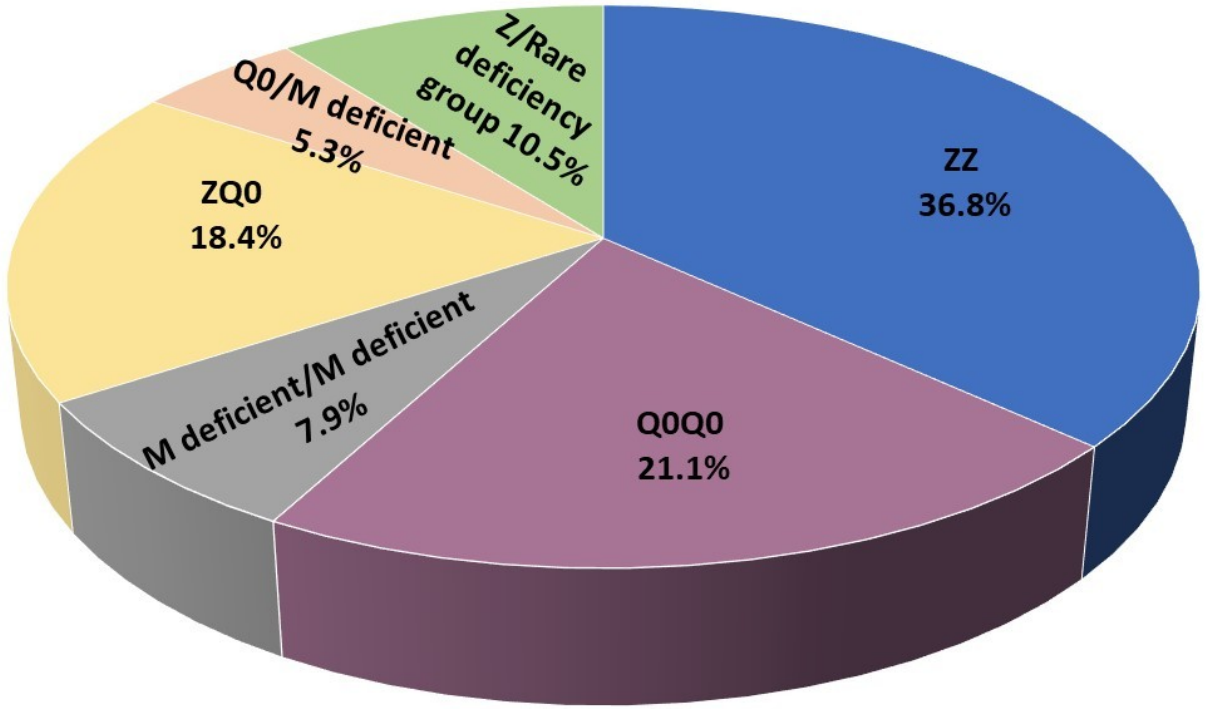
Background

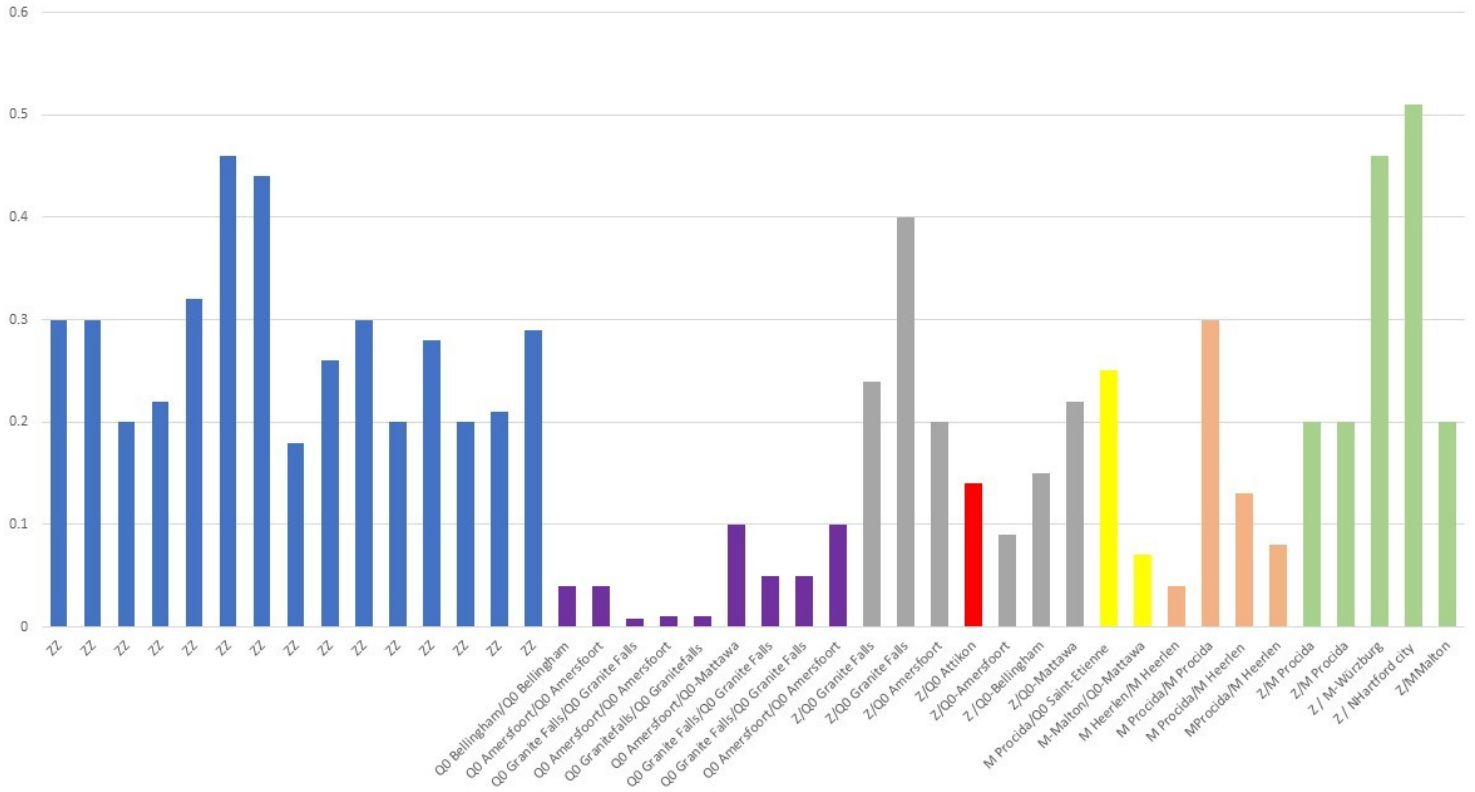
- ✓ A1Antitrypsin (AAT) is the major protease inhibitor in serum and severe AAT deficiency (AATD) worldwide relates mainly to the homozygous state of the PI*Z variant



- ✓ 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

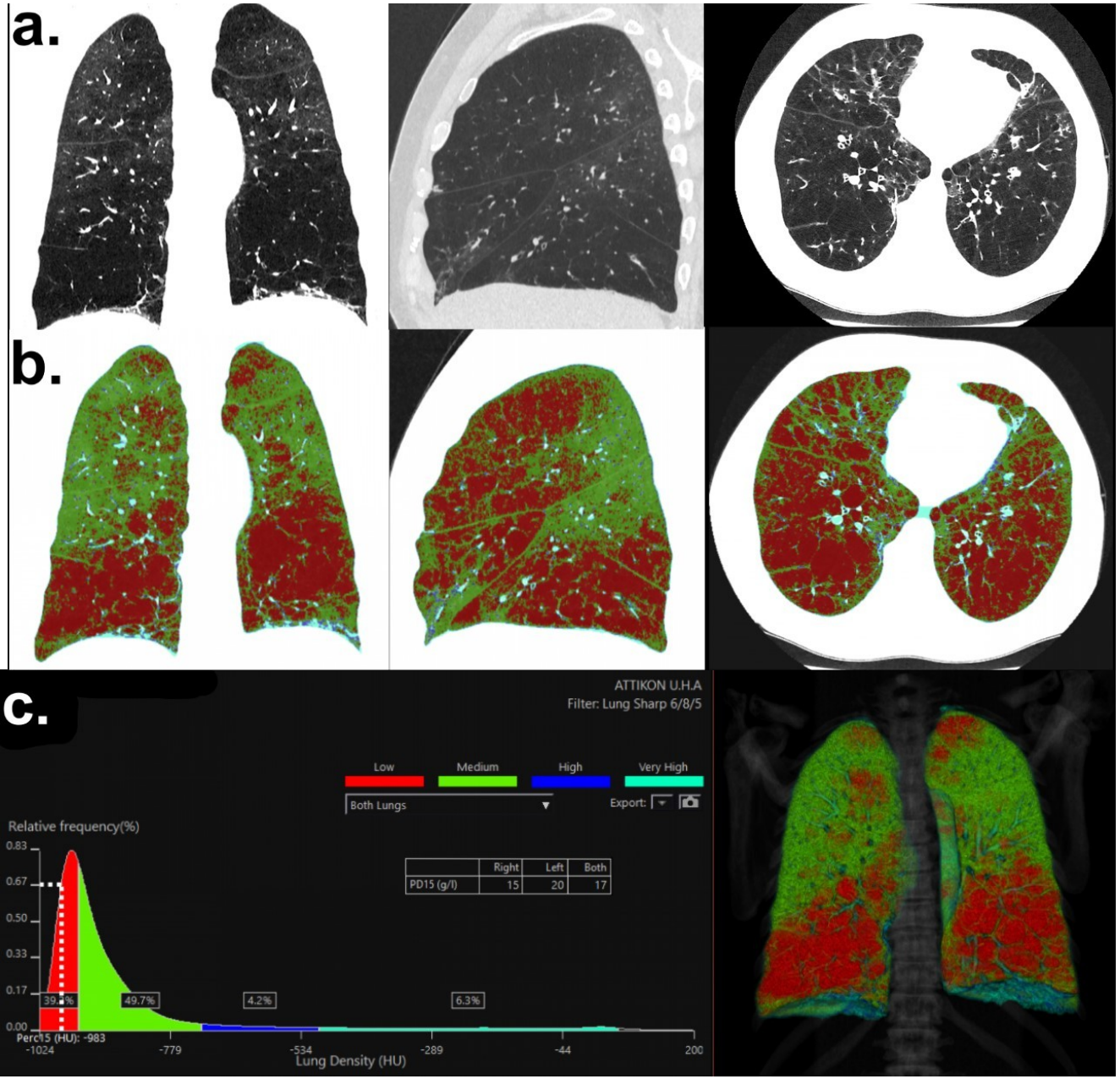
Papiris SA, et al. Pulmonology 2023; in press

The Greek rare variants embraced the null PI*Qo$_{Bellingham}$, PI*Qo$_{Amersfoort}$, PI*Qo$_{Granite\ Falls}$, PI*Qo$_{Saint\text{-}Etienne}$, PI*Qo$_{Mattawa}$; and the deficient variants PI*M$_{Heerlen}$, PI*M$_{Procida}$, PI*M$_{Malton}$, PI*M$_{Würzburg}$, and PI*N$_{Hardfordcity}$; rarities were observed also in heterozygous, PI*MQo$_{Amersfoort(M1Ala)}$, PI*MM$_{Procida}$, PI*MP$_{Lowell.}$(p.Asp280Val), PI*MO$_{Feyzin}$



The epitome of rarities in AATD in Greece was the discovery of a novel variant named Q0$_{Attikon}$ (c.1A>G; p.Met1?)

Papiris SA, et al. Pulmonology 2023; in press



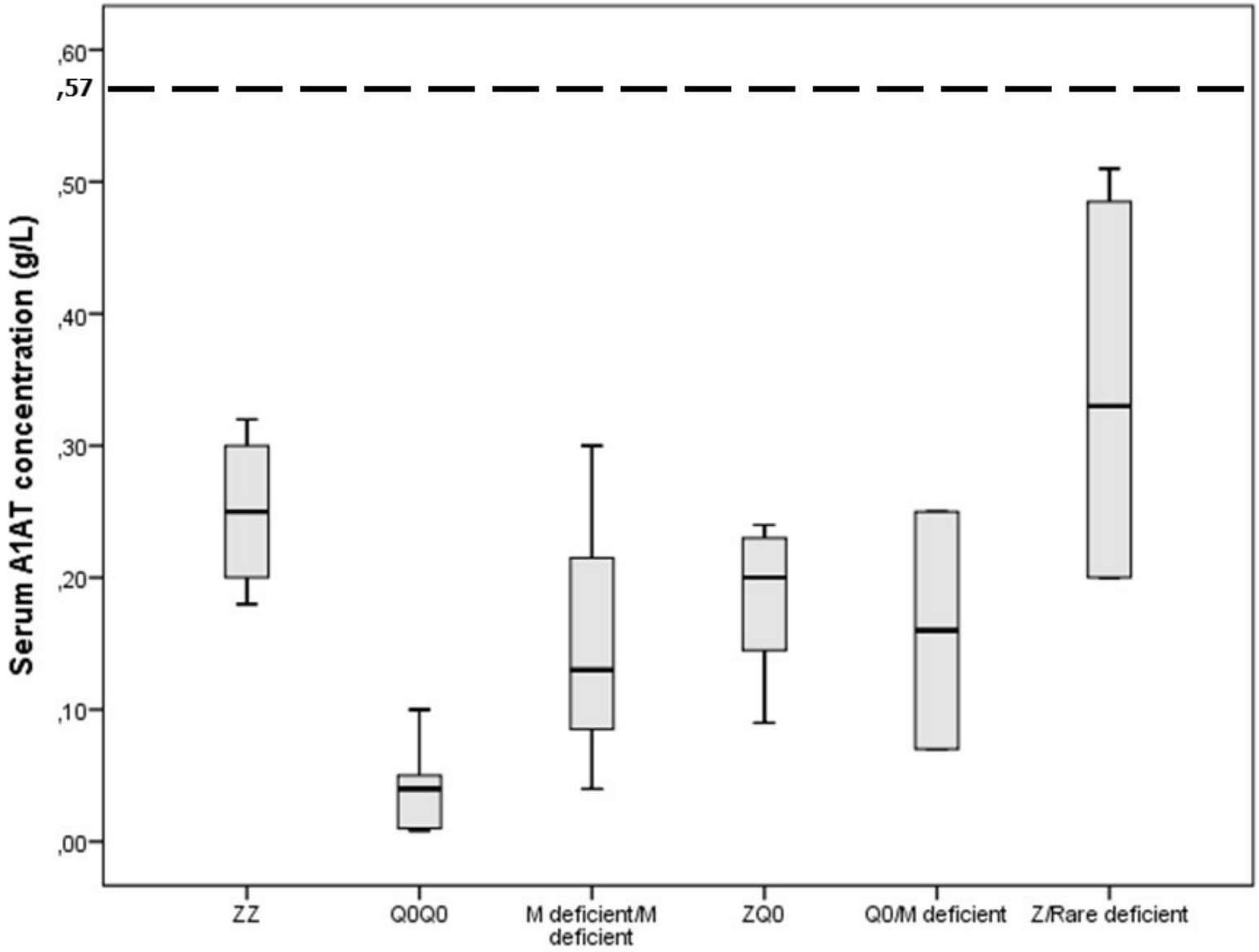
✓ A 55 year-old non-smoker male, no family history,
no significant environmental exposures

✓ Early-age emphysema and bronchiectasis and asthma

✓ Severe and repetitive exacerbations

- Red-colored pixels represent attenuation lower than <-950HU, c: Lung density distribution graph. PD15 = -983HU shows an estimated pulmonary density of 17g/L (for both lungs).
- the percentage of emphysema (areas of low-attenuation) was estimated ~ 44,2% for both lungs

- ✓ On admission, the values of FEV_1 %, FVC%, FEV_1/FVC, DLCO% were 37, 85, 34.8 and 53 respectively.
- ✓ AAT serum levels by nephelometry were 0.14g/L (0.9-2.0g/L) [CRP at 2.7mg/L(0-5mg/L]
- ✓ chronic obstructive lung disease in a non-smoker in a background of severe AATD.



International Journal of Chronic Obstructive Pulmonary Disease Dovepress
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METHODOLOGY

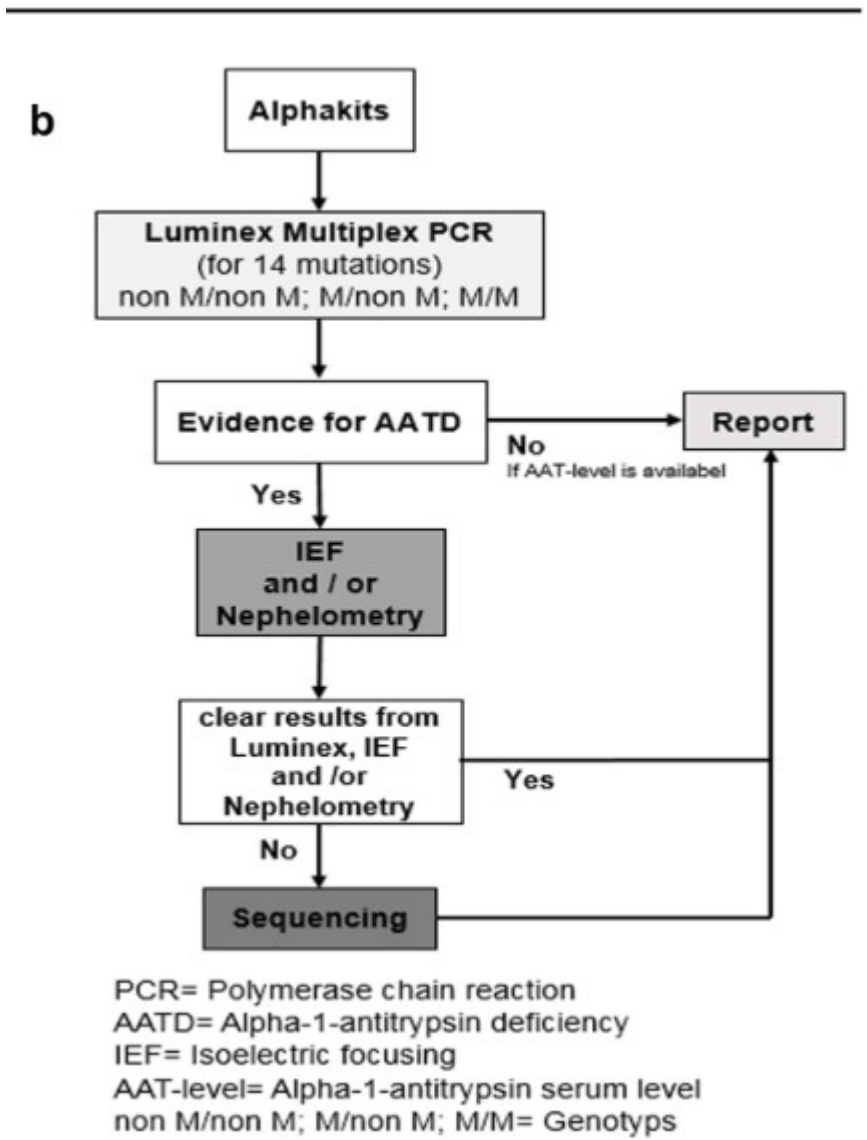
Diagnosing Alpha-1-Antitrypsin Deficiency Using A PCR/Luminescence-Based Technology

This article was published in the following Dove Press journal:
International Journal of Chronic Obstructive Pulmonary Disease

Table 1 Allelic Variants And Associated Alleles Which Were Tested With The AAT Genotyping Kit

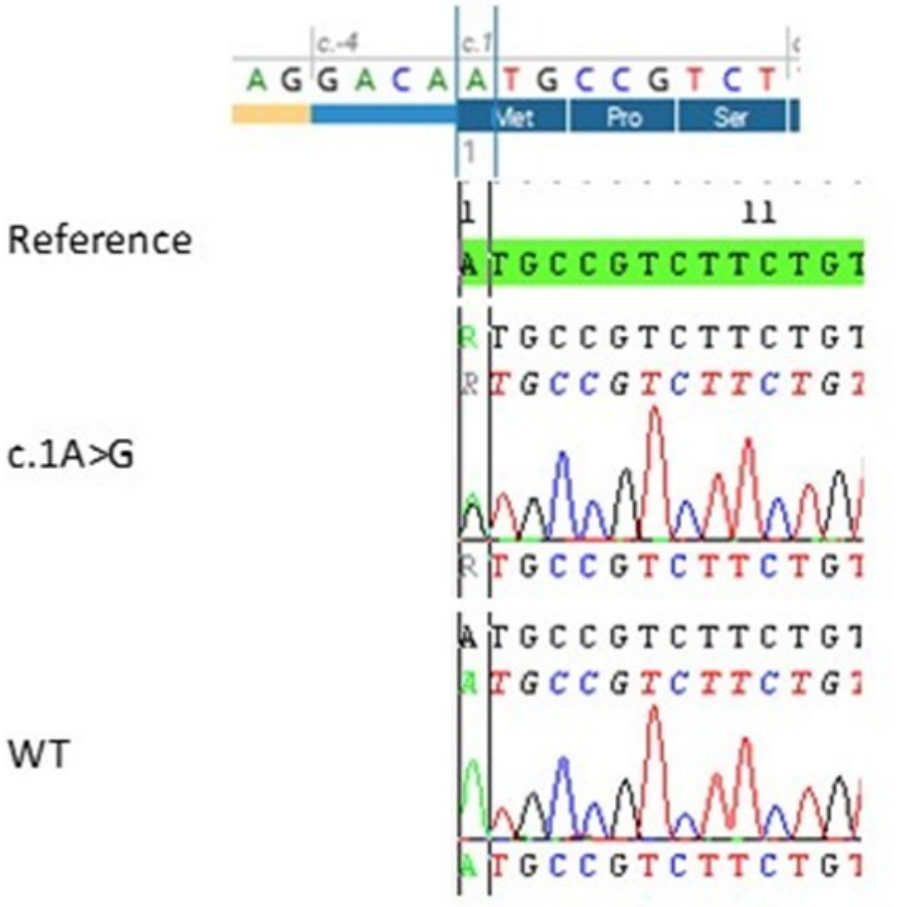
Allelic Variant	Associated Alleles	Predicted Protein Activity
c.187C>T	PI*I	Reduced (mild)
c.194T>C	PI*M procida	Reduced (severe)
c.226_228delTTC	PI*M malton, PI*M palermo, PI*M nichinan	Reduced (severe)
c.230C>T	PI*S iiyama	Reduced (severe)
c.551_552delC	PI*Q0 granite falls	None (no protein)
c.647G>T	PI*Q0 west	None (no protein)
c.721A>T	PI*Q0 bellingham	None (no protein)
c.739C>T	PI*F	Reduced (mild)
c.839A>T	PI*P lowell, PI*P duarte, PI*Q0 cardiff, PI*Y barcelona	Reduced (mild)
c.863A>T	PI*S	Reduced (mild)
c.1096G>A	PI*Z	Reduced (severe)
c.1130_1131insT	PI*Q0 mattawa, PI*Q0 ourem	None (no protein)
c.1156_1157insC	PI*Q0 clayton, PI*Q0 saarbruecken	None (no protein)
c.1178C>T	PI*M heerlen	Reduced (severe)

Note: This kit uses multiplex PCR and Luminex xMAP-technology to detect 14 types of AATD mutations simultaneously.



Veith M, Int J Chron Obstruct Pulmon Dis. 2019; 14:2535–2542, Ottaviani S, et al. J Clin Lab Anal. 2020 ;34(7): e23279

- ✓ **The test confirmed the presence of Z allele in heterozygosity. On the IEF gel, only the Z-protein could be identified, suggesting an additional null mutation based on the discrepancy between the very low levels of AAT and the genotype and phenotype findings so far.**
- ✓ **this new variant, identified by Next Generation Sequencing (NGS) and confirmed by Sanger sequencing, affected the translation initiation codon (Met1) completely inhibiting AAT production**



SAMPLE INFORMATION

Sample code (patient):	31313	**Sample reception date:**	2020-12-10
Sample lab code:	20AA6241	**Sample report date:**	2021-01-14
Sample type:	DBS		

SAMPLE RESULTS

Sequencing of SERPINA1 (NM_001127701.1) full gene was carried out and the following variants are detected:

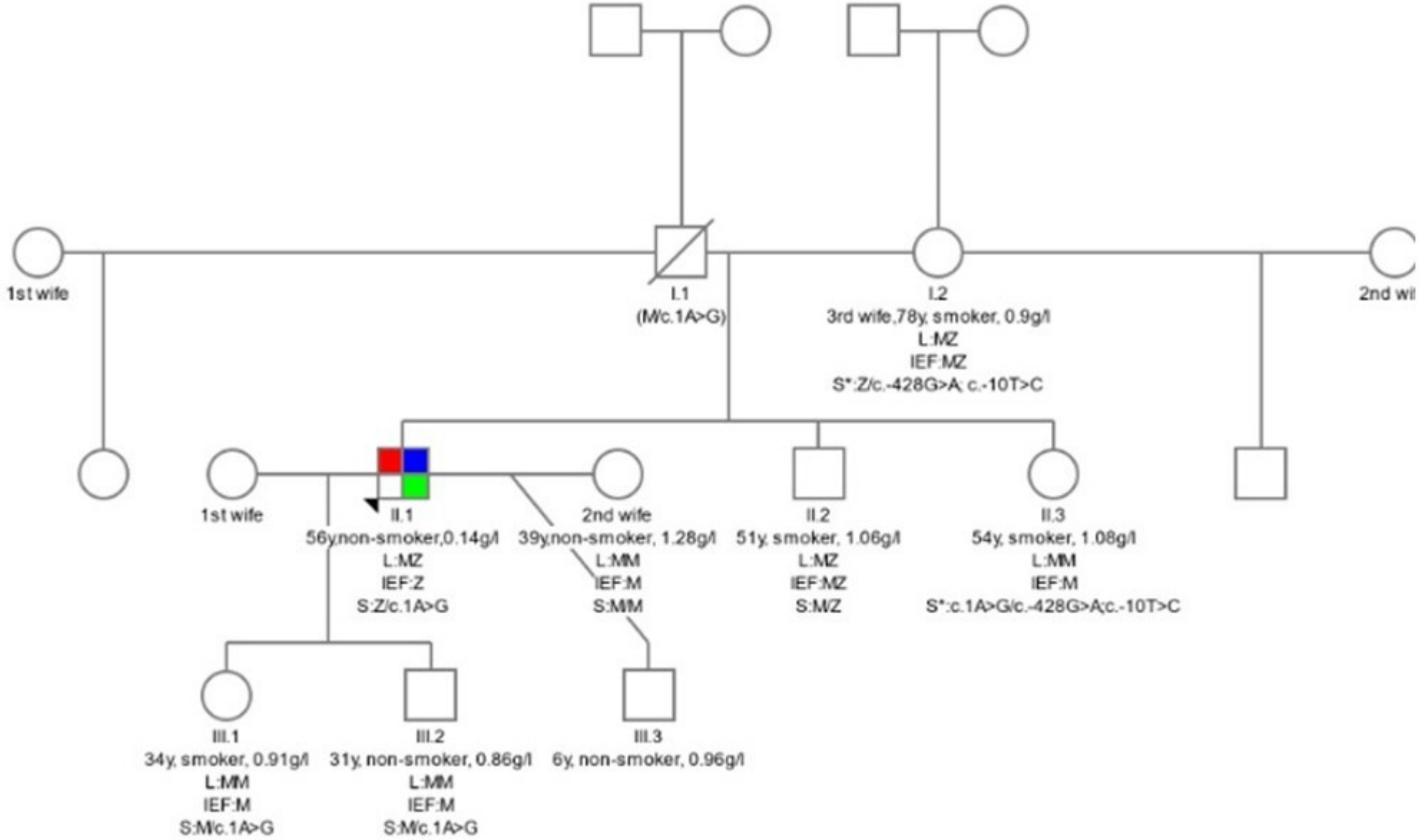
Status	Heterozygous	Heterozygous
Genome position (GRCh38)	g.94378610	g.94383237
Nucleotide change	c.1096G>A	c.1A>G
Aminoacid change	p.(Glu366Lys)	p.Met1?
Aminoacid change (alternative name) in the mature protein	Glu342Lys	p.Met(-24)?
Mutation type	Aminoacid change	Substitution
Associated allele	PI* Z	ND
Predicted protein activity	Reduced (severe)	Unknown
Pathogenicity	Pathogenic	Unknown
SNP code	rs28929474	rs1057516555
ClinVar code	17967	370522
Reference	Turino et al (1996) Am J Respir Crit Care Med. 154 (6 Pt 1):1718-25; Ogushi et al (1987) J Clin Invest. 80(5):1366-74; Chappell et al (2008) Hepatology. 47(1):127-32	ND
Associated allele (other names)	PI* Z(AUGSBURG), PI* Z(TUN)	ND
exon (NM_001127701.1)	exon7	exon4

- ✓ The new variant was named from the University-Clinic and Hospital of discovery **Pi*Qo$_{Attikon}$**.
- ✓ The new variant proved clearly pathogenic a high **REVEL score of 0.759** (range 0-1)
- ✓ in association with the clinical presentation of the patient and the very low levels of AAT
- ✓ Further discussion in a web-based multidisciplinary meeting dedicated to AATD (www.respifil.fr) confirmed the above conclusions.

RespiFIL
Filière Maladies Respiratoires Rares

RCP déficit sévère en alpha 1 antitrypsine du 05/05/2022

☒ *« Je déclare avoir recueilli le consentement de mon patient pour le passage de son dossier en Réunion de Concertation Pluridisciplinaire (RCP) et l'avoir informé que ses données de santé sont gérées via un site sécurisé et sont partagées avec d'autres professionnels de santé à des fins de prise en charge diagnostique et thérapeutique, et peuvent être utilisées à des fins de recherche clinique ».*


1st wife
I.1
(M/c.1A>G)
I.2
3rd wife,78y, smoker, 0.9g/l
L:MZ
IEF:MZ
S*:Z/c.-428G>A, c.-10T>C
2nd wi
1st wife
II.1
56y,non-smoker,0.14g/l
L:MZ
IEF:Z
S:Z/c.1A>G
2nd wife
39y,non-smoker, 1.28g/l
L:MM
IEF:M
S:M/M
II.2
51y, smoker, 1.06g/l
L:MZ
IEF:MZ
S:M/Z
II.3
54y, smoker, 1.08g/l
L:MM
IEF:M
S*:c.1A>G/c.-428G>A,c.-10T>C
III.1
34y, smoker, 0.91g/l
L:MM
IEF:M
S:M/c.1A>G
III.2
31y, non-smoker, 0.86g/l
L:MM
IEF:M
S:M/c.1A>G
III.3
6y, non-smoker, 0.96g/l

Conclusions

- ✓ The characterization of a new null variant of *SERPINA1* named from 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 never been identified before. Gene sequencing was necessary for genetic diagnosis.
- ✓ additional investigation is necessary regarding the clinical phenotype expressed from carriers of rare variants; a project that fulfills the European Alpha-1 Research Collaboration (EARCO) consortium
- ✓ In the future the detection of rare genotypes by widening AATD spectrum and geographic distribution of variants may add to understand the anthropologic evolution of its mutations and probably to personalize preventive and therapeutic measures.

Amos Cassioli, *Lorenzo dei Medici mostra a Galeazzo Sforza le suppellettili artistiche da lui raccolte*, 1868, Olio su tela, 193 × 290 cm, Siena, Banca Monte dei Paschi di Siena, collezione Chigi Saracini, Foto Claudio Giusti

Thank you very much- Grazie Mille