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COMMENT

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Risk of lung disease with the Pi*SS genotype of alpha-1 antitrypsin: the evidence in context

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To the editor,

We read the recent study by Martín et al. with interest [1]. Evidence regarding the clinical implications on the Pi*SS genotype of alpha-1 antitrypsin deficiency (AATD) has been historically scarce and additional information is always welcome. The authors present an analysis of the EARCO registry to compare Pi*SS to what they describe as the most frequently encountered severe genotypes: Pi*SZ and Pi*ZZ (hereinafter referred to as SS, SZ, ZZ, etc.). The authors conclude that individuals with the SS genotype demonstrate lower prevalence of lung disease than ZZ individuals, but similar to SZ. We would however highlight some aspects of this work, and add some further points of information, which we feel are crucial to drawing an informed opinion on this topic.

Registry data is essential to research activities in rare conditions and as such EARCO is an invaluable asset. It should be noted however, that registry data is particularly prone to ascertainment bias, which if not accounted for can lead to skewed interpretations. Previously, in a multivariate analysis of MZ, SZ and ZZ individuals, lung-index status (diagnosis due to lung disease or symptoms) accounted for approximately $15\%_{\text{predicted}}$ lower forced expiratory volume in 1 s ($FEV_{1\%\text{predicted}}$), even when accounting for tobacco smoke exposure [2]. This issue should be a particular point of consideration in the study by Martín et al. As the authors point out, the MS genotype of AAT is highly common, occurring as frequently as 1/10 persons in some populations [3, 4]. Consequently, the SS genotype is at least 2–4 times as prevalent as ZZ, and yet in this study the SS cohort is ten times smaller than that of ZZ individuals. This raises concerns of selection (ascertainment) bias, and therefore questions over the generalisability of these results. While the authors make great efforts to propensity score match these individuals, this would not circumvent the issues around generalisability if ascertainment bias was significant at the point of recruitment into EARCO.

Further to this point, the authors state that to their knowledge this is the largest reported cohort of SS individuals to date, with 56 included. However, in 2020 Nakanishi et al. reported the largest ever cohort of 1013 SS individuals in a multi-genotype analysis of UK Biobank participants comparing MZ, SS, SZ and ZZ AATD to 398,424 MM controls (i.e., non-deficient wild-type AAT). As evidenced by the results in both the main paper and supplementary results, no difference in risk of COPD or mortality was detected in SS individuals compared to MM individuals. Crucially, the findings regarding risk of COPD remained true regardless of smoking status. The sample size reported by Nakanishi et al. is a significant strength, and making the findings the most generalisable data regarding the SS genotype published to date.

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These clarifications matter, as the authors have suggested that in their study, SS smokers were similar to SZ smokers, and at the same time make reference to the SZ genotype as a "*severe*" form of AATD. Readers could therefore conclude that SS demonstrated similar features to a severe AATD genotype, and be led to think of it as equivalent. This notwithstanding the fact that the much larger study by Nakanishi, of over 1000 SS individuals, demonstrated no difference in risk compared to MM controls, let al.one SZs. These factors together risk propagating misunderstandings of this nuanced this area. The evidence regarding the implications of the SZ genotype has evolved significantly in recent years and at there is now little evidence to support that assertion that SZ results in "severe" deficiency by any clinically meaningful metric [2, 5]. The Nakanishi study provided useful evidence in the SZ genotype too, boasting the largest reported cohort to date, at 867 [6].

To summarise, in the absence of cigarette smoking, SZ has not been associated with an increased risk of lung disease compared to MM controls [5, 6]. Furthermore, even in association with tobacco smoking, lung function and outcomes are similar to moderate deficiency states such as MZ [2] and SS [1], and far removed the significant morbidity and mortality associated with the ZZ genotype [2]. The persisting misperception of SZ AATD and a severe state of deficiency is likely driven by the fact that many SZ individuals will display AAT levels under the "*putative protective threshold*" of 11 µm (or 0.57 g/dL) [5, 7]. However, as has been previously summarised, there has never been any evidence that serum AAT levels below a threshold of 11 µm are associated with worse outcomes in the SZ genotype and indeed the data refute this hypothesis [8].

It is particularly concerning then that in the discussion, Martín et al. raise the prospect of a possible role for intravenous alpha-1 augmentation (IV-AAT) in select SS individuals, on the basis of an observed similarity between SZ smokers and SS smokers in their study. IV-AAT therapy was devised to raise circulating serum levels above 11µM [9], and levels below this threshold are seen in around 40% of individuals with the SZ genotype [5]. Consequently, SZ-AATD is included in the licensing indications for IV-AAT, however the benefits of intravenous augmentation have never been formally studied in this genotype, let al.one the SS genotype. To suggest that there may be a role for IV-AAT for an unlicensed and unstudied genotype such as SS which is less deficient than even SZ raises concerns and should be discouraged, especially given the potential for this statement to be interpreted as a conflicted when companies which produce IV-AAT replacement therapies fund the EARCO registry through unrestricted funding.

In summary, we commend Martin et al. on their work, which adds to the knowledge around the SS genotype. We believe the results generally support the mounting evidence from numerous other publications, which is that MZ, SS and SZ genotypes are all moderate deficiency states, highly distinct from ZZ and other rarer genotypes associated with severe deficiency. However, we urge that greater care be taken when discussing "severe" states of AATD, and strongly suggest the SZ genotype should no longer be described as a severe deficiency of AAT, given the now substantial evidence to the contrary.

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H.OB wrote the manuscript. C.M and A.F conceptualised the commentary and edited the manuscript. All authors reviewed the final manuscript.

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