Understanding at-risk subgroups for lung function impairment in life-long nonsmokers with α_1-antitrypsin deficiency

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The association of α_1-antitrypsin deficiency with emphysema and chronic obstructive pulmonary disease (COPD) was first described in 1964 [1]. However, it was not until 1976 that uncommon coding variants in the gene encoding α_1-antitrypsin (*SERPINA1*) were identified as the cause, specifically variants at amino-acid positions 288 ($Glu^{288}Val$ or protease inhibitor (PI) type S) and 366 ($Glu^{366}Lys$ or PI type Z) [2, 3]. Over the past 40 years, the role of *SERPINA1* genetic variation and α_1-antitrypsin deficiency as a risk factor for emphysema and COPD has become well established for individuals with a history of tobacco smoke exposure who are homozygotes with two copies of these variants (PI ZZ and SS) and compound heterozygotes with PI types Z, S (PI ZS) or other pathogenic PI types [4–6]. However, it is unclear whether α_1-antitrypsin deficiency determines the risk for lung function impairment in individuals without a critical gene by environment interaction with tobacco smoke exposure.

Early studies have shown a subgroup of PI ZZ homozygote never-smokers that experience a greater decline in FEV1 than what would be expected in the general population. Although the underlying risk factors for this at-risk subgroup are unclear, data from longitudinal cohorts suggest that at least one PI type Z allele could be sufficient to contribute to an accelerated decline in lung function in an appropriate subgroup [6]. For instance, in the Lung Health Study and the Copenhagen Heart Study, PI MZ subjects had an increased rate of decline in FEV1 compared to the more common MM genotype; however, this association was not observed in a general population from Tucson, Arizona [7–9]. More recently, a longitudinal study of a Swiss general population demonstrated that a subgroup of PI MZ heterozygotes who were obese or with increased markers of systemic inflammatory showed an accelerated decline of the maximal mid-expiratory flow rate (MMEF), a putative marker of small airways disease (SAD) [10]. Cumulatively, these data suggest that a subgroup of PI MZ individuals develop impaired small airways function, which is a postulated precursor to emphysema, thus providing the rationale for a novel predictive marker of lung function impairment and emphysema in PI ZZ homozygotes.

In an article published in this issue of the *European Respiratory Journal*, Stockley *et al.* [11] stratified 196 PI ZZ homozygote never-smokers from the ADAPT cohort based on the presence of SAD (maximal mid-expiratory flow (MMEF) <80% of predicted) and baseline airflow obstruction based on GOLD criteria

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for COPD (forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) ratio of <0.7). No subject had baseline airflow obstruction or computed tomography (CT) scan-based emphysema without evidence for SAD. In all subjects without baseline airflow obstruction (FEV_1/FVC >0.7), FEV_1 and FEV_1/FVC were slightly lower in the subgroup with SAD than in the subgroup without SAD, and the health quality of the former subgroup was significantly worse. Most importantly, the annualised rate of decline of FEV_1 was accelerated in the subgroups with SAD, irrespective of the presence of baseline airflow obstruction. In a subset of 109 PI ZZ homozygotes (the vast majority with MMEF<80% of predicted), subjects with overt CT evidence of emphysema had markedly reduced MMEF measures, less than 20% of predicted, while those without emphysema showed high inter-individual variability in MMEF measures.

These results suggest that dysfunction of the small airways is present in the early history of α_1-antitrypsin deficiency, even in life-long nonsmokers, and thus provides the rationale for a more sensitive test (compared to conventional spirometric measures) to detect an at-risk ZZ homozygote subgroup with baseline airflow obstruction or emphysema. Small airways (less than 2.0 mm in diameter) offer negligible resistance to airflow in healthy subjects (<20% of the total lower airway resistance), but their resistance may increase 4–40 times in COPD [12, 13]. Because the patency of the small airways depends heavily both on their own intrinsic structure and on the radial traction exerted by the surrounding alveolar walls, the loss of radial traction due to a primitive destruction of alveolar septa may cause small airways to collapse, inducing small airway alterations [14]. At the same time, a primitive dysfunction of the small airways may lead to mechanical uncoupling between the small airways and the surrounding alveoli, followed by disarrangement of the alveolar architecture [15]. McDonough and colleagues found a markedly reduced number of terminal bronchioles in resected specimens from lungs of prior smokers with centrilobular or panlobular emphysema. In these specimens, the volumetric density of terminal bronchioles was decreased in lung regions in which alveolar dimensions were normal, suggesting that small airway injury precedes the development of emphysema [16].

In individuals with a history of smoking, early small airways dysfunction is expected, because small inhaled particles preferentially deposit in the small airways due to the local decrease of velocity secondary to the increase in the total cross-section [17]. This results in repetitive chemical injury, as immune cells are increasingly recruited to the site of airways deposition, resulting in chronic inflammation and airway remodelling [18]. In addition, chronic mechanical damage can exacerbate small airway injury, as remodelling, surfactant inactivation and loss of elastic recoil may enhance the collapsibility of small airways, and cyclical airway closing and reopening can ensue. This cyclic process has been shown to induce epithelial necrosis and sloughing, ruptures of bronchiolar–alveolar attachments, as well as aggravating inflammation in animal models [15].

Could small airway dysfunction precede overt emphysema in the absence of an inflammatory stimulus such as tobacco smoke in the periphery of the tracheobronchial tree? In the absence of pathological studies in PI ZZ homozygotes with a life-long absence of tobacco smoke exposure, one can only speculate that weakening of the elastic fibres in the peripheral airways could be the primitive event triggering the architectural disruption manifested in panlobular emphysema. Alternatively, early bronchiolar–parenchymal uncoupling not detectable by quantitative CT has the potential to cause airways distortion and instability before diffuse alveolar damage becomes evident. Extensive bronchiolar–alveolar uncoupling and marked shortening of pre-terminal bronchioles suggestive of disruption of the longitudinal elastic fibres has been described in microCT of emphysematous lungs in donors with α_1-antitrypsin deficiency, but a significant tobacco smoking history complicates this interpretation, as it prevents a direct translation of these findings to this current study of life-long nonsmokers [19–21].

The application of MMEF as a marker of SAD in airways disease and in the subgroup evaluated in the current study is not beyond scrutiny, as clearly outlined in an editorial previously published in the *European Respiratory Journal* [20]. MMEF is not unequivocally associated with small airways resistance and collapsibility, and has a broad normal range in the healthy population. As the lower limit of normality of MMEF for 50- to 60-year-old subjects (<60% predicted) is much lower than the arbitrarily chosen cut-off of 80% predicted used in this study, subjects without SAD may have been misclassified, explaining the limited capability of MMEF to predict FEV_1 decline. Fortunately, FVC was not different among the three experimental groups, which excludes the confounding effect of FVC change on MMEF interpretation [21]. The implications of these findings are also limited to a very uncommon subgroup of PI ZZ homozygotes (genotype frequency of PI type Z homozygotes was 0.1% (TT, rs28929474) in "Whites" from the NIH National Heart Lung and Blood Exome Variant Server (EVS)), thereby limiting its applicability to the broader general population [22]. However, the implications for these effects of *SERPINA1* variation would be more significant if, indeed, PI Z heterozygotes (CT genotype frequency of 3.2% in the EVS) without a history of cigarette smoking could also be at risk for airflow limitation or emphysema that could be detected by evidence for SAD [10, 22].

Early studies have recognised that only a subgroup of PI ZZ individuals experience an accelerated decline in lung function, and in the current study, only a subgroup had small airways disease or baseline airflow obstruction. Although a proportion of these inter-individual differences could be age-related, additional risk factors should be considered in cohorts with minimal tobacco smoke exposure. First, critical environmental exposures such as minimal tobacco smoke exposure or environmental pollution could be associated with an accelerated FEV1 decline, as was demonstrated in rescue workers from the World Trade Center collapse with α_1-antitrypsin deficiency [23]. Second, airways diseases such as asthma are common in α_1-antitrypsin deficiency, and might influence lung function in asthmatics, providing a rationale for recommendations from the American Thoracic Society and European Respiratory Society to test for α_1-antitrypsin deficiency in asthmatics with irreversible airflow obstruction [24–26]. Third, multiple genes from genome-wide association studies (GWAS) in large general-population consortia (*HHIP*, *FAM13A*, *GSTCD* and *AGER*) have been associated with baseline lung function and could have cumulative, detrimental effects in individuals with an increasing number of risk variants [27–29]. In addition, variants in genes in the α-mannosidase pathway that regulate α_1-antitrypsin degradation were associated with CT-based emphysema in a multi-ethnic GWAS, resulting in gene–gene interactions that could influence lung function [30]. Finally, in PI MZ individuals from the general population, an accelerated decline in small airways function was only observed in a subgroup with increased systemic inflammation or obesity, a subgroup that warrants further study [10].

This study suggests that small airways function impairment identifies a small subgroup of PI ZZ individuals that have an accelerated decline in lung function and increased airflow obstruction, despite the absence of a history of cigarette smoking. Further study of physiological, environmental and genetic risk factors in additional, well-characterised cohorts, including PI MZ heterozygotes, will be required for targeted precision medicine approaches in all individuals with α_1-antitrypsin deficiency for the prevention and early management of emphysema and COPD.

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