SERPINA1 PiZ and PiS heterozygotes and lung function decline in the SAPALDIA cohort

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BACKGROUND: Severe alpha1-antitrypsin (AAT) deficiency is a strong risk factor for COPD. But the impact of gene variants resulting in mild or intermediate AAT deficiency on the longitudinal course of respiratory health remains controversial. There is indication from experimental studies that pro-inflammatory agents like cigarette smoke can interact with these variants and thus increase the risk of adverse respiratory health effects. Therefore, we tested the effect of the presence of a protease inhibitor (Pi) S or Z allele (PiMS and PiMZ) on the change in lung function in different inflammation-exposed subgroups of a large, population-based cohort study.METHODOLOGY AND PRINCIPAL FINDINGS: The SAPALDIA population includes over 4600 subjects from whom SERPINA1 genotypes for S and Z alleles, spirometry and respiratory symptoms at baseline and after 11 years follow-up, as well as proxies for inflammatory conditions, such as detailed smoking history, obesity and high sensitivity C-reactive protein (hs-CRP), were available. All analyses were performed by applying multivariate regression models. There was no overall unfavourable effect of PiMS or PiMZ genotype on lung function change. We found indication that PiZ heterozygosity interacted with inflammatory stimuli leading to an accelerated decline in measures in use as indices for assessing mild airway obstruction. Obese individuals with genotype PiMM had an average annual decline in the forced mid expiratory flow (?FEF25-75%) of 58.4 ml whereas in obese individuals with PiMZ it amounted to 92.2 ml (p?=?0.03). Corresponding numbers for persistent smokers differed even more strongly (66.8 ml (PiMM) vs. 108.2 ml (PiMZ), p?=?0.005). Equivalent, but less strong associations were observed for the change in the FEV1/FVC ratio. CONCLUSIONS: We suggest that, in addition to the well established impact of the rare PiZZ genotype, one Z allele may be sufficient to accelerate lung function decline in population subgroups characterized by elevated levels of low grade inflammation.
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