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Rare α_1-antitrypsin genotype in a grass seed worker

To the Editor:

We hereby present a case of chronic obstructive pulmonary disease (COPD) caused by a combination of occupational dust exposure and severe α_1-antitrypsin (α_1-AT) deficiency. On evaluation of the genetics of this severe α_1-AT deficiency, an apparent PiMM genotype was revealed to be heterozygotic for two different rare deficient alleles.

In 2008, a 62-year-old man was referred to Dept of Occupational Medicine, Aalborg University Hospital, Aalborg, Denmark, by his general practitioner (GP) to assess whether his reduced lung function was related to occupational dust exposure. For 26 years, he had been employed at a factory that produces grass seed, predominantly from rye grass. The factory received grass seeds from farmers in a dried condition, which were then cleaned and packed in bags for resale. Grass seeds were loaded as loose seeds, and mechanically cleaned, filtered and sorted. During the first 10–15 years of his employment, the process caused heavy dust development, especially when the grass seeds were cleaned but also when the cleaned seeds were weighed. From the early 1990s, the dust filters were improved on the cleaning machine, but still, a considerable dust exposure was reported. However, dust measurements were never performed. The staff did not wear dust masks or other protective equipment. In later years, grass seed handling was automated, including weighing and packing of seeds. The worker had part-time administrative work during the last few years, but he did spend a few hours in the plant every day. He continued working until his retirement in 2012. He had no other dust exposure and he was a social smoker until the mid-1980s, with a cumulative tobacco consumption of 3–4 pack-years. He had no prior history of asthma or other lung diseases. In 2000, he contacted his GP due to increasing exertional dyspnoea and an episode of near-syncope. He was hospitalised in the Dept of Cardiology without any abnormal findings. In 2002, radiography showed a flattened diaphragm. Lung function testing was carried out by the GP for the first time in 2008 and identified significant obstruction, and he was referred for an occupational health assessment. Besides dyspnoea, he showed no asthma symptoms, cough or expectoration, and no aggravation at work. On clinical examination, we observed slight exertional dyspnoea upon walking up one flight of stairs but no dyspnoea at rest. He had a hyperexpanded chest but normal auscultation. Lung function tests showed an obstructive pattern with forced vital capacity (FVC) 4.3 L (96% predicted), forced expiratory volume in 1 s (FEV_1) 1.9 L (55% predicted) and FEV_1/FVC ratio 0.43, and peak flow 252 $L \cdot min^{-1}$ (49% predicted). Blood test showed a severely reduced α_1-AT level (0.13 $g \cdot L^{-1}$, reference range 0.9–2.0 $g \cdot L^{-1}$). Skin-prick testing showed no signs of allergy. Genetic testing was performed first by looking for Z or S genotypes, but the patient was reported to be Pi*MM. Therefore, sequencing [1] was performed after DNA extraction from a dry blood spot. Final genotype was reported to be Pi*MmaltonMheerlen. He was reported to the Danish National Board of Industrial Injuries for workers' disability compensation for the COPD diagnosis and recognised as having a 20% disability. He was further referred to a lung department where he was treated with a combined inhaled corticosteroid and long-acting β_2-agonist and enrolled in a trial of substitution with human α_1-AT *versus* placebo. He gave consent for publication as a case report.

A gene–environment interaction is a condition in which a genetic vulnerability in a subject in combination with harmful environmental factors causes illness or impairment of the individual. α_1-AT deficiency has been suspected to be an inherited disorder of the lung since 1963 [2]. Before modern genetic tests were invented, gel electrophoresis was used to investigate the variants of α_1-AT, characterised by M-, S- and

Z-bands. In blood tests for α_1-AT, homozygotic, normal samples (PiMM) will show normal protein levels (0.9–2.0 g·L^{-1}), while Pi*ZZ will reflect a homozygous defective protein with levels of 0.1–0.5 g·L^{-1} [3]. However, new genotyping methods have revealed more polymorphisms in the *SERPINA1* gene. Some of these are M-like variants, showing the same electrophoretic properties as M. Both Mmalton and Mherleen are deficient variants and show decreased α_1-AT levels when present in heterozygosity with normal variant M [4]. α_1-AT deficiency is a rare condition and accounts for only 1% of COPD cases [5]. In Switzerland, the frequency of the Z-allele has been estimated to be 1.3%, whereas any rare alleles have been estimated at 0.3% in the general population [6]. Based on this information, the prevalence of having any two rare alleles would be less than one in 10^5. However, there are substantial geographical differences in *SERPINA1* polymorphisms [7] and no valid information of rare alleles in Denmark is available. Organic dust is a well-known contributor to the development of COPD. The population-attributable risk of work-related COPD has been estimated to be $\geqslant$15% [5, 8]. However, a lot of dust-exposed individuals will never develop COPD, as is the case for smokers. These differences in susceptibility could be due to genetic factors. α_1-AT deficiency is one of the most important genetic contributors to COPD, as the Pi*ZZ genotype is the most frequent genotype entailing severe COPD, and occupational exposures have been shown to have negative impact on lung function in α_1-AT-deficient subjects with the Pi*ZZ [9, 10] and PI*MZ [11] genotypes. In this case, the severe α_1-AT deficiency (blood α_1-AT level 0.13 g·L^{-1}) has been shown to be due to a rare genotype, Pi*MmaltonMheerlen. Testing for α_1-AT deficiency is important in all patients with COPD [12], even when there are exposures known to be sufficient as an independent risk factor. A two-step evaluation should be carried out: measuring levels of AAT and sorting out the genetics. Genetic testing of Pi genotype alone (M, S, and Z) would have led to the wrong diagnosis.

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Case study: COPD caused by combined grass dust exposure and α_1-antitrypsin deficiency due to two rare alleles http://ow.ly/ABAu7

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