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Identification of a novel alfa1- antitrypsin genotype as a result of a familial screening.

Katarzyna Duk[1], Małgorzata Czajkowska-Malinowska[2], Aneta Zdral[1], Beata Szumna[1], Joanna Chorostowska-Wynimko[1]
[1]National Institute of Tuberculosis and Lung Diseases, Department of genetics and clinical immunology , Warszawa, Poland
[2]Kujawsko-Pomorskie Centrum Pulmonologii, , Bydgoszcz, Germany

Alpha1-antitrypsin deficiency is an autosomal codominant disease characterized by reduced serum activity/concentration of alpha1-antitrypsin (A1AT) due to changes in the SERPINA1 gene coding sequence. Apart from the most prevalent PI*S and PI*Z A1AT deficiency variants, other so-called rare variants also predispose to severe chronic respiratory disorders such as emphysema and chronic obstructive pulmonary disease. Importantly, the currently recommended diagnostic algorithm consists of serum concentration assessment and targeted genotyping or A1AT protein phenotyping. Therefore it does not allow for the straightforward detection of rare mutations, as direct sequencing of *SERPINA1* is not routinely performed.

Here we present the case report of the 61-old male, ex-smoker suffering from COPD, who was for A1AT deficiency diagnostic. According to the routine protocol, the A1AT protein was measured in serum by nephelometry revealing borderline A1AT concentration of 89 mg/dl (reference range 88-183 mg/dl). Following AA1T phenotyping performed by means of immune isoelectric focusing was interpreted as a normal MM-phenotype. Next, genotyping towards two most common mutations of the SERPINA1 gene (PI*Z, PI*S) was performed by real-time PCR. No PI*S and PI*Z allele was detected. Due to clinical symptoms observed as well as A1AT concentration at the lower limit of the reference value the more detailed examination of SERPINA1 exons II–V was performed by direct sequencing in search for the rare A1AT allelic variants. Surprisingly, the Sanger sequencing of *SERPINA1* gene revealed two deficiency variants the rare one: PI*PDonauworth (c.1093G>A; p.Asp341Asn) and the common PI*Z (c.1096G>A; p.Glu342Lys) that was not detected either by geno- or phenotyping. In order to explain this apparent discrepancy a familial A1AT deficiency analysis was performed with two close family members. Analysis of brother"s sample revealed no abnormalities, while in mother"s decreased A1AT serum concentration (77 mg/dl); MM-like phenotype and identical aberrations in exon V: PI*PDonauworth and PI*Z. Therefore, it was concluded that PI*PDonauworth and PI*Z were situated on the same allele, in cis position.

This is the very first report of cis-colocalization of the two *SERPINA1* mutations rare and common in two related subjects. Identification of a novel genotype was possible only through the analysis of familial mutation segregation.