Pediatric respirology and hereditary disorders

Frequency of rare alpha-1-antitrypsin variants in a group of Polish patients with chronic respiratory disorders

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Background:

A1AT deficiency is a genetic disorder caused by mutations in SERPINA1 gene. There are over 120 variants of the A1AT, including at least 60 known clinically meaningful mutations encoding biologically deficient protein. The two most common deficiency alleles PI*S and PI*Z can be easily identified by combination of serum A1AT measurement and phenotyping. However, rare variants, such as PI*Mmalton, are difficult to detect with routine laboratory tests. PI*Mmalton is a deletion of a TTC codon in exon II (p.F51del or p.F52del), resulting in low A1AT serum concentration with clinical presentation similar to severe deficiency phenotypes as PI*ZZ. However, it is characterized by normal isoelectric pattern and consequently high risk of misdiagnosis. According to current data, PI*Mmalton is relatively highly prevalent in Southern Mediterranean area. It's frequency in Polish population is unknown.

The aim of the study was to evaluate frequency of rare AATD variants, in particular PI*Mmalton, in a group of Polish patients referred to the National Reference AATD Lab due to the chronic respiratory disorder.

Methods:

Test results of 1033 patients referred for AATD diagnostics between January 2014 to September 2015 were reassessed for rare AAT variants detected by isoelectrofocusing (IEF). Next, 100 subjects were selected according to preset criteria: normal (PI*MM) phenotype identified by IEF and A1AT serum concentration < 120 mg/dl as measured by nephelometry. SERPINA1 gene was analyzed in their blood samples by Sanger direct sequencing method.

Results:

890 out of 1033 samples (86%) carried the normal PI*MM genotype, whereas in 143 samples (14%) at least one A1AT deficiency variant was detected. 11 rare variants of SERPINA1 were detected, including 5 cases of PI*F (c.739C>T) and 4 cases of PI*I (c.187C>T). In one individual $M2_{Obernburg}$ (c.514G>T) mutation was detected, in another SERPINA1 non-pathogenic mutation c.922G>T. No PI*Mmalton mutation was identified in examined group.

Conclusion:

Our data suggest very low incidence of PI*Mmalton mutation in Polish population. There is a need for further research to validate the diagnostic algorithm for rare AAT mutations detection.