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Title: Influence of ADRB2 gene polymorphism on cold airway hyperresponsiveness and asthma control depending on inhaled glucocorticoids use

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Body: Previously published data suggest an association between c.46A>G SNP of ADRB2 gene, functional activity of β_2-adrenergic receptors (β_2-AR) and cold airway hyperresponsiveness (CAH) in patients with bronchial asthma (BA). Objective: We aimed to investigate the impact of inhaled glucocorticosteroids (ICS) on the clinical state and CAH in BA patients depending on the c.46A>G (rs1042713) variants of ADRB2 gene. Methods: 136 mild to moderate Caucasian asthmatics with mean age 37±10 were recruited. All the patients were assessed for asthma control, previous ISC use and underwent 3-min isocapnic cold air hyperventilation (ICAH) challenge. Genotyping of the SNP was performed by PCR-RFLP analysis. Results: ICS users number and daily dosage were comparable among distinct genotypes. AA homozygotes who did not receive therapy proved to have lower ACT score (14 (11; 14) vs. 18 (16; 19), p<0.001) and excessive FEV1 fall after the ICAH (-22 (-51; -15) vs. -2,2 (-6.8; 1.08), p<0.001) in comparison with GG homozygotes. On the contrary, ICS users did not show such associations. Relations of their CAH level and disease control to genotype were not statistically significant. CAH prevalence was greater among AA homozygotes and decreased substantially if they received ICS treatment (p=0.01) while therapeutic effect on CAH in GG patients was not so noticeable. Conclusions: The obtained results indicate diminished activity of β_2-AR in the examined AA carriers as they more frequently exhibited CAH and had poorer asthma control. ICS therapy can reverse depressed β_2-AR function in spite of the genetically induced defect and therefore provides particular benefit in AA patients.