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Title: Role of -511C>T/+3953C>T haplotypes of IL1B gene as risk factors of COPD

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Body: COPD is multifactorial lung disease driven by abnormal inflammatory reaction. Therefore, inflammatory mediators are considered to be of distinct importance in pathogenesis of COPD. It is well recognized that the genetic factors play a role in susceptibility to COPD. Hence, polymorphisms in pro-inflammatory cytokines may confer a risk for the development of COPD. There are several case-control studies focused on the role of some of the described SNPs in IL1B in COPD, however no previous study has been conducted to evaluate the role of haplotypes of -511C>T and +3953C>T in IL1B as risk factors of COPD. The aim of the current study was to investigated the role of the haplotypes of the -511C>T and +3953C>T in IL1B as candidate risk factors of COPD in Bulgarian population. We genotyped 163 patients with COPD and 174 control individuals using Taqman genotyping assay for IL1B -511C>T SNP and PCR-RFLP-based method for +3953C>T SNP. The frequencies of the IL1B haplotypes of the studied two loci of IL1B (-511C>T and +3953C>T) did not differ significantly between controls and COPD patients (p=0.099). However, the T_C haplotype, constructed by alleles found to determine enhanced expression of IL-1β, appeared to be associated with higher risk of COPD (OR 1.25, 0.88-1.79, p=0.231) compared to the most common C_C haplotype and with 1.70-fold higher risk of COPD (95% CI, 1.10-2.64, p=0.018) compared to the C_T haplotype, previously associated with lower IL1B expression. Based on the results of the current study for the first time we propose that the T_C haplotype of IL1B-511C>T:+3953C>T, supposed to determine enhanced expression of IL-1b, is a predisposing factor for COPD in Bulgarian population.