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Title: Proteinase activated receptor-1 (F2R) polymorphisms and susceptibility to exacerbations in COPD

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Body: Introduction: COPD is a condition of global importance, characterized by accelerated lung function decline and an abnormal inflammatory response. Exacerbations (i.e. episodes of acute deterioration of respiratory health) account for much of the morbidity and mortality in COPD. The reasons why some patients are more susceptible to exacerbations is poorly understood, but familial clustering suggests that there may be a genetic basis. Proteinase activated receptor-1 (PAR_1) activation leads to the generation of several inflammatory mediators involved in COPD and our unpublished data have shown that functional polymorphisms of PAR_1 are protective in sarcoidosis. Aims & objectives: The aim of this study was to investigate whether PAR_1 polymorphisms are associated with COPD exacerbation frequency (ExF). Methods: Two PAR_1 SNPs (rs2227744 and rs32934) and a 13bp in/del (rs11267092) were genotyped in 136 infrequent and 67 frequent exacerbators. Results: The genotypic distributions of all polymorphisms were in Hardy-Weinberg equilibrium. The rs2227744 SNP showed a statistically significant association with ExF. Frequency of the minor allele was 0.47 in infrequent and 0.37 in frequent exacerbators (OR 1.5, 95%CI 1.0-2.4, p=0.04). Considering exacerbations as a continuous variable, the presence of the minor allele was associated with a significantly lower exacerbation rate (3.03 vs 1.98 exacerbations/year, MWU p=0.04). Conclusions: Taken together with our previous studies showing that the presence of the minor allele at SNP rs2227744 increases PAR_1 expression, these data suggest that this SNP may confer a degree of protection against exacerbations in COPD by increasing PAR_1 expression. Funded by the BLF.