European Respiratory Society
Annual Congress 2013

Abstract Number: 1558
Publication Number: 1526

Abstract Group: 12.3. Genetics and Genomics
Keyword 1: Genetics Keyword 2: Asthma - mechanism Keyword 3: Asthma - management
Title: Pharmacogenetics in severity of bronchial hyperresponsiveness in asthma

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Body: Introduction Treatment with inhaled corticosteroids (ICS) reduces bronchial hyperresponsiveness (BHR), a core feature of asthma. Not all asthmatics show the desired treatment response. Genetic variability is an important determinant of therapeutic efficacy of ICS. Aim To identify genes that alter the response of BHR to ICS in asthma. Methods Out of the 920 asthmatics in the Dutch Asthma GWAS, 650 with complete data were included. A genome wide interaction study (GWIS) using linear regression was performed on BHR severity (ln(slope dose-response curve)) with interactions between SNPs and ICS, adjusted for smoking. Significance was reached when: 1. p<10-4 for interaction, or 2. p<10-3 for the interaction combined with p<10-4 on the main effect of the SNP in either the ICS treated or untreated group. Results ICS treated asthmatics (n=426) had significantly better BHR than non ICS treated asthmatics (n=224). 26 SNPs had a significant ICS interaction and 28 had a combination of significant interaction and main effect. Three top-hits were located near ADAMTS12 (fig. 1). These SNPs were associated with more severe BHR in subjects with ICS. Conclusion In total, 54 SNPs altered the response to ICS with regard to the severity of BHR in asthmatics. Replication in two independent cohorts will be performed to confirm these results. Figure 1: Top-hit rs4867517, individuals with ICS use and ADAMTS12 variant have more severe BHR than those without ICS (mean±sem).