Abstract: Genetic variants in Protocadherin-1, bronchial hyperresponsiveness and asthma subphenotypes in German children

Body: Background: Recently, Protocadherin-1 (PCDH1), located on chromosome 5q31-33, in the vicinity of the cytokine gene cluster containing several known candidate genes for asthma and allergy (interleukin-4, interleukin-5, interleukin-13 and RAD50), was reported as a novel susceptibility gene for bronchial hyperresponsiveness (BHR) and asthma. Objectives: We aimed to define linkage disequilibrium (LD) between the region comprising PCDH1 and the cytokine gene cluster. Next, for a comprehensive analysis of the PCDH1 locus we conducted detailed fine mapping of the PCDH1 region and investigated effects of single nucleotide polymorphisms (SNPs) in BHR, asthma and related phenotypes. Methods: Genotype information was acquired from Illumina HumanHap300Chip genotyping, MALDI-TOF MS genotyping and
imputation. Associations were investigated in a population of at least 1,303 (651 asthmatics) from two
german study populations (MAGICS and ISAAC II). Results: No relevant LD between 14 PCDH1 tagging
SNPs and 98 SNPs within the cytokine cluster was detected. There were no significant associations with
BHR, atopy, allergic rhinitis and atopic eczema. However, rs7719391 was associated with asthma
(OR=0.85, p=0.039) and non-atopic asthma (OR=0.69, p=0.009). The exonic SNP rs3797054 previously
reported to be associated with BHR and asthma, was significantly associated with non-atopic asthma
(OR=0.70, p=0.019) in our study. Significant associations with non-atopic asthma were observed also for
rs11167761 (OR=1.54, p=0.021), rs3935792 (OR=1.32, p=0.039), rs2974704 (OR=0.43, p=0.009).
Conclusions: PCDH1 polymorphisms may specifically affect the development of non-atopic asthma in
children. These authors contributed equally: Mrs. Antoaneta Toncheva, Dr. Kathrin Suttner, and Mr. Sven
Michel.