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Title: SNPs in SPINK5 gene region are associated with asthma severity: Preliminary results from the gene environment interactions in respiratory diseases (GEIRD) study

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Body: Aim: The present analysis is aimed at assessing the genetic polymorphisms associated with asthma severity through a candidate gene study. Methods: We evaluated 331 subjects (aged 20-64) with asthma, who were identified from the general population between 2008 and 2010 in Verona, in the clinical stage of an Italian multi-centre (multi)case-control study (GEIRD). A panel of 384 Tag-SNPs, which are representative of 69 candidate genes with a previous indication of a possible association with asthma/COPD/rhinitis, was genotyped by a custom GoldenGate Genotyping Assay. An asthma severity score (mean=3.4, range: 0-26; high values represent severe conditions) was computed by a multiple correspondence analysis on the basis of self-reported asthma-like symptoms in the past year and lung function. The association with the severity score was tested separately for each SNP by a gamma regression model, adjusting for the use of inhaled drugs for respiratory problems in the past year. Results: Three SNPs in linkage disequilibrium (LD) (min $r^2=0.95$) in the SPINK5 gene region were significantly associated with asthma severity:

Genotypic association analysis

SNP	rs4357026		rs1862439		rs3777143	
genotype	C/C or C/G	G/G	T/T or C/T	C/C	A/A or A/G	G/G
n° of subjects	287	42	279	37	288	40
mean score	3.6	1.8	3.7	1.9	3.5	1.9
p-value*	0.000036		0.000113		0.000109	

corrected p-value**	0.014	0.044	0.042
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* adjusted for the use of inhaled drugs for respiratory problems in the past year; ** obtained by multiplying the p-value by 384 according to the Bonferroni correction

Conclusion: Our preliminary results suggest that SPINK5 or genes in LD play a role in asthma severity in adults.