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Title: Genetic variations in the TLR signaling pathway are associated with childhood asthma

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Body: Background: Common single nucleotide polymorphisms (SNPs) in Toll-like receptors (TLRs) are associated with asthma and atopy, but very little is known about the relevance of SNPs in TLR regulatory and downstream signaling pathway molecules. Objective: To systematically analyze the association between SNPs in TLR signaling pathway genes and childhood asthma and atopy. Methods: Common SNPs present in TLR signaling pathway were retrieved from HapMap database and LD analyses were performed to determine tagging SNPs. Association of 375 tagging SNPs with asthma were analysed in a genome wide association (GWA) dataset consisting of 651 asthmatics and 652 controls. SNPs were genotyped by

Illumina HumanHap300Chip (n=169) or MALDI-TOF MS (n=19) or imputed (n=187). Algorithms were applied to rank associations and clustering of the associated genes on a virtual pathway map was performed by a systems biology approach and we assessed the putative functional relevance of associated SNPs by in silico analysis. Results: We identified 41 genes involved in the TLR signaling and regulatory pathways, harbouring 1405 SNPs (tagged by 375) with minor allele frequency >5% in the HapMap (CEU) population. SNPs located in 19 genes showed association with asthma at a significance level of at least $p<0.05$. Top ranked asthma-associated genes (e.g. IRAK-1, MKK-3, and ERK-2) mapped to distinct functional clusters within the TLR pathway and associated SNPs were located in promoter (n=16), intronic (n=116) and downstream regions (n=16). Conclusion: SNPs in TLR signaling network genes show association with asthma and distinct clusters are associated with atopic and non-atopic asthma.