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Title: Gene polymorphisms, gene expression and inflammatory markers in preschool children with and without wheeze

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Body: Background: Although exact mechanisms underlying preschool wheeze are largely unclear, immune responses are likely to be involved. Aims and objectives: We employed an integrative genomic approach relating gene polymorphisms, mRNA expression, and products in exhaled breath condensate (EBC) of markers involved in airway inflammation to each other and to recurrent wheeze in preschool children. Methods: From the Asthma DEtection and Monitoring (ADEM) study, 202 children with recurrent wheeze (≥2 episodes, ISAAC questionnaire) and 50 healthy controls aged 2-4 years (mean 3.2 years) were included. Genetic variants, gene expression and protein levels of interleukin (IL) 4, IL8, IL10, IL13, Tumour Necrosis Factor alpha (TNFa) and Intercellular Adhesion Molecule 1 (ICAM1) were analysed in saliva or buccal cells (DNA), blood (RNA), and EBC. Statistical analysis was performed by logistic and linear regression. Results: ICAM1 rs5498 A-allele was positively related to recurrent wheeze (p=0.02) and to increased mRNA expression of ICAM1 (p=0.01) which in turn was positively associated with soluble (s)ICAM-1 in EBC (p=0.04). sICAM-1 in EBC was elevated in recurrent wheezers (p=0.03). IL10 polymorphisms rs1800872 and rs1800896 were associated with decreased IL10 mRNA expression (p<0.01). In EBC levels of IL4, IL10, and IL13 in EBC were elevated in recurrent wheezers compared to healthy controls (all p=0.01). Conclusions: We studied several inflammation markers at different levels which may allow causative interpretation. This study indicates that ICAM1 associates as a significant marker

in preschool wheeze.