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Title: Transcriptome analysis of controlled and problematic severe childhood asthma

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Body: Asthma, characterised by symptoms such as coughing, wheezing and shortness of breath, is the most common chronic disease in children. A subgroup of patients suffer from problematic severe asthma with chronic symptoms and/or severe exacerbations despite treatment with several drugs. We have used cap analysis of gene expression (CAGE) and small RNA sequencing to compare the blood transcriptomes of children with controlled asthma (n=15), problematic severe asthma (n=15) and age-matched healthy controls (n=10). Pathway analyses of genes differentially expressed between these groups highlight differences in chemokine and interleukin signalling, as well as regulation of the actin cytoskeleton with effects on leukocyte migration and adhesion. Children with controlled and problematic severe asthma also appear to differ in activation of the innate immune system with differential expression of genes involved in the response to bacterial infection and natural killer cell-mediated cytotoxicity. A number of putative novel genes and transcript isoforms are also found among the differentially expressed genes. The nucleotide-level resolution of transcriptional start sites of the CAGE data enables detailed analysis of promoter usage. By integrating transcriptome data to identify differences in the regulation of gene expression between children with controlled asthma and problematic severe, as well as healthy controls we hope to deepen the understanding of the immunobiology of asthma and identify pathways that could present new targets for therapy. The ready availability of blood samples also makes this material excellent for development of clinically useful biomarkers.