# Epigenomewide Association Study Identifies DNA Methylation Markers for Asthma Remission

C. Xu[1], D. A. van der Plaat[2], C. Qi[1], H. M. Boezen[2], J. M. Vonk[2], G. H. Koppelman[1]; [1]Department of Pediatric Pulmonology and Pediatric Allergology, University of Groningen, University Medical Center Groningen, Groningen, Netherlands, [2]Department of Epidemiology, University of Groningen, University Medical Center Groningen, Groningen, Netherlands.

**Corresponding author's email: c.xu@umcg.nl**

Rationale Asthma is a chronic respiratory disease, and it is treatable but not curable. However, some patients experience spontaneous asthma remission. The mechanisms of remission are still unknown. We hypothesized that epigenetic mechanisms may be involved in asthma remission. Methods We assessed DNA methylation levels at 436,824 CpG sites (CpGs) from whole blood derived from 44 subjects with persistent asthma and 28 subjects with asthma remission (1) using the Infinium HumanMethylation 450 BeadChip array. Clinical asthma remission was defined as the absence of asthma symptoms and no use of asthma medication for at least 12 months, whereas complete remission also included subjects with normal lung function and absence of airway hyperresponsiveness. CpGs related to asthma remission were identified using robust linear regression with adjustment for age, sex, smoking history, batch variables and estimated white blood cell counts. Moreover, we further tested the differentially methylated CpGs obtained from blood in nasal brush respiratory epithelial cells of 44 subjects with persistent asthma and 53 subjects with asthma remission. We replicated our significant findings in whole blood DNA in the LifeLines cohort (2) including 99 subjects with persistent asthma and 25 subjects with clinical asthma remission, and also assessed the methylation levels of the replicated CpGs in 636 healthy controls. Results For clinical remission, we identified seven differentially methylated CpGs in blood that mapped to eight genes (TMEM30B, SLC38A6, LACRT, ICMT, PEX11B, SNRPD1, ACBD5, MKS1) at epigenome-wide statistical significance (p value$< 1.14 \times 10^{-7}$). We replicated findings for cg13378519 in LifeLines at p value $= 3.57 \times 10^{-5}$ which passed Bonferroni-corrected statistical significance (Fig.1). Subjects with clinical remission had lower methylation levels of cg13378519 in blood and nasal epithelial cells compared to persistent asthmatics. The methylation status of asthma remission is not equal to that of healthy controls (Fig.1). Cg13378519 is located in the promoter region of PEX11B (peroxisomal biogenesis factor 11 beta). Overexpression of PEX11B in human cells was found to induce peroxisome proliferation. Conclusions This is the first study on differential methylation across the genome in relation to asthma remission in whole blood with independent replication. Our findings indicate a possible role of the peroxisome proliferator-active receptor as being involved in asthma remission. References 1. Carpaij OA et.al. Eur Respir J. 2017 Jun 1;49(6). 2. Stolk RP et.al. Eur J Epidemiol. 2008 Jan;23(1):67-74.

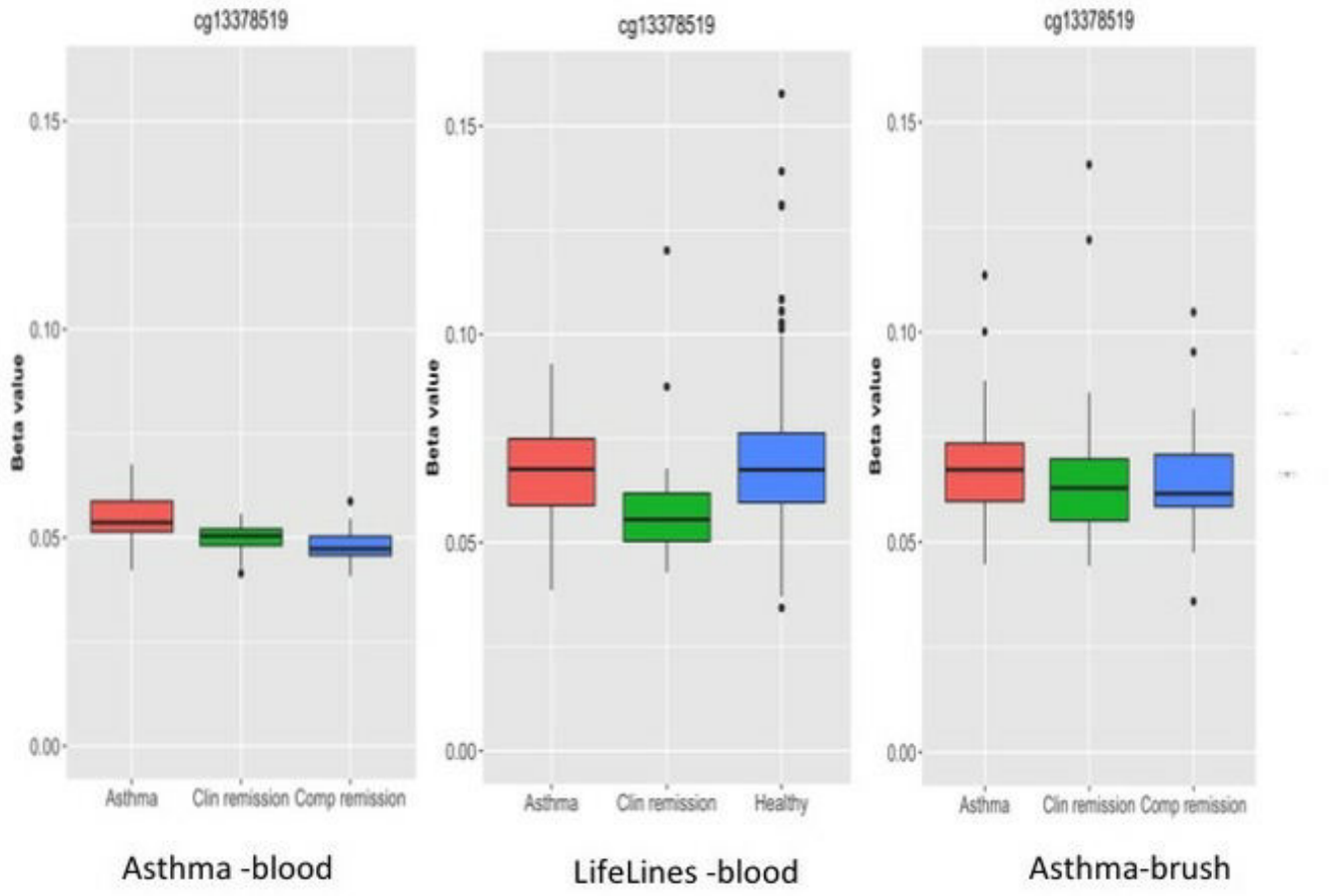


Fig1. Box plots of DNA methylation levels of cg13378519 in three studies.

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