

Quantitative Methylation–Expression Correlation and Epigenetic Biomarker Discovery in Asthma

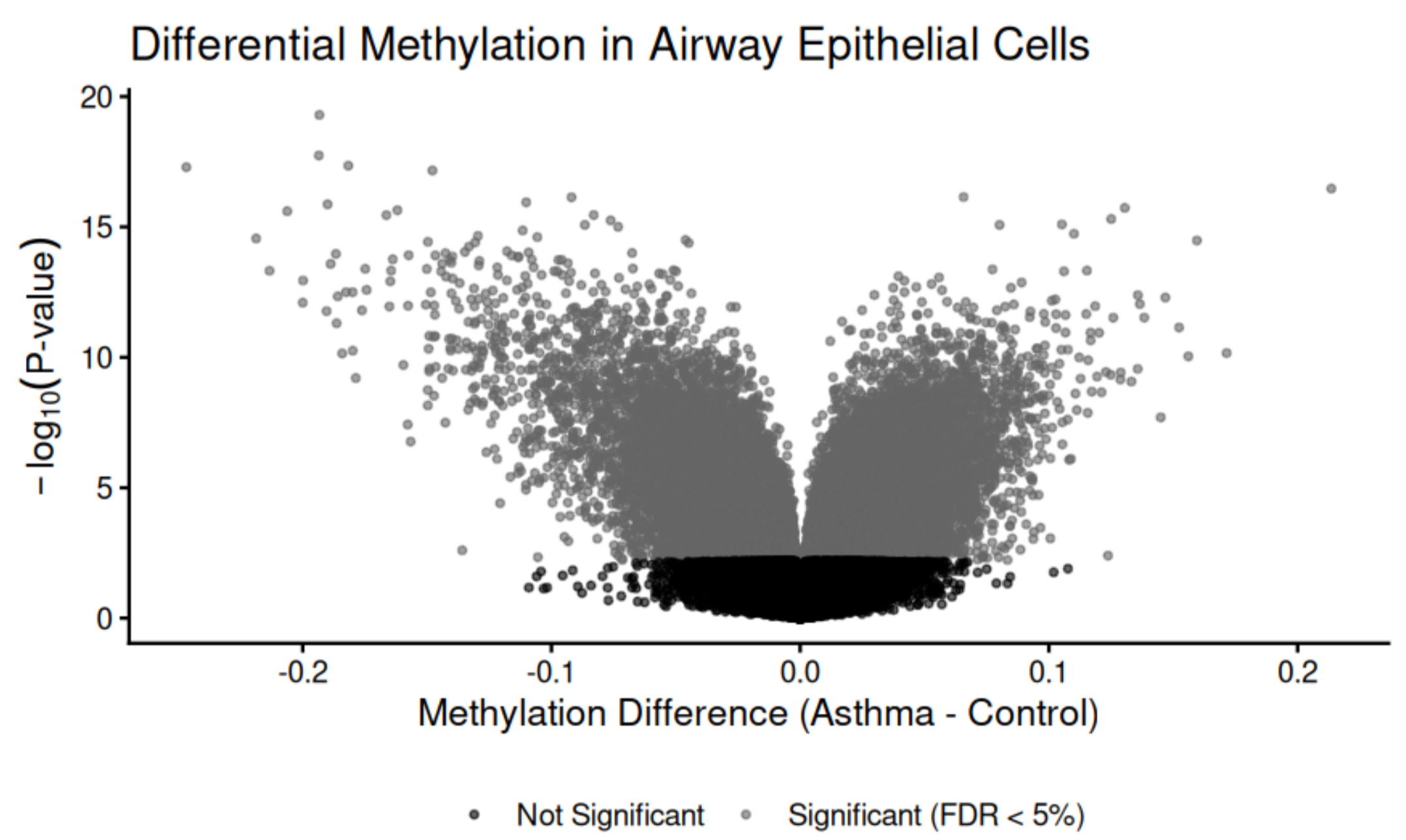
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Introduction

We investigated how DNA methylation and gene expression jointly shape asthma biology by integrating multi-omics data from airway epithelial cells. Through benchmarking, correlation analysis, and pathway enrichment, we show that methylation changes persist despite steroid-normalized transcriptomes. This decoupling enables identification of stable epigenetic biomarkers and explains inconsistencies with classical gene signatures.

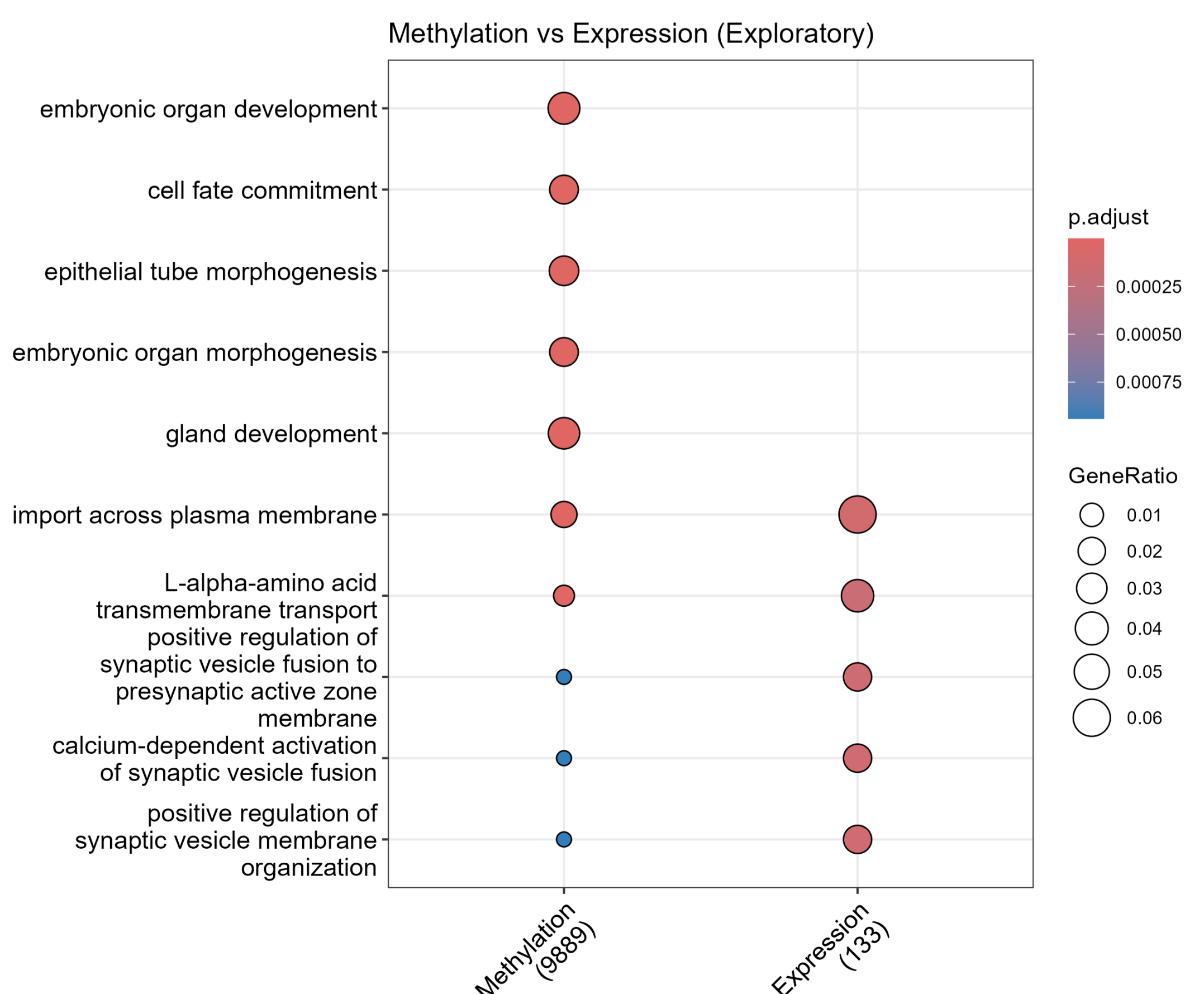
Widespread Hypomethylation in Asthma Airway Epithelium

- In the analysis of endobronchial airway epithelial cells, the majority of the outlier CpGs are hypo-methylated (skewed to the left)
- P values go as as low as 10^{-15} , indicating that there is a lot of statistical significance in methylation differences between case and control.



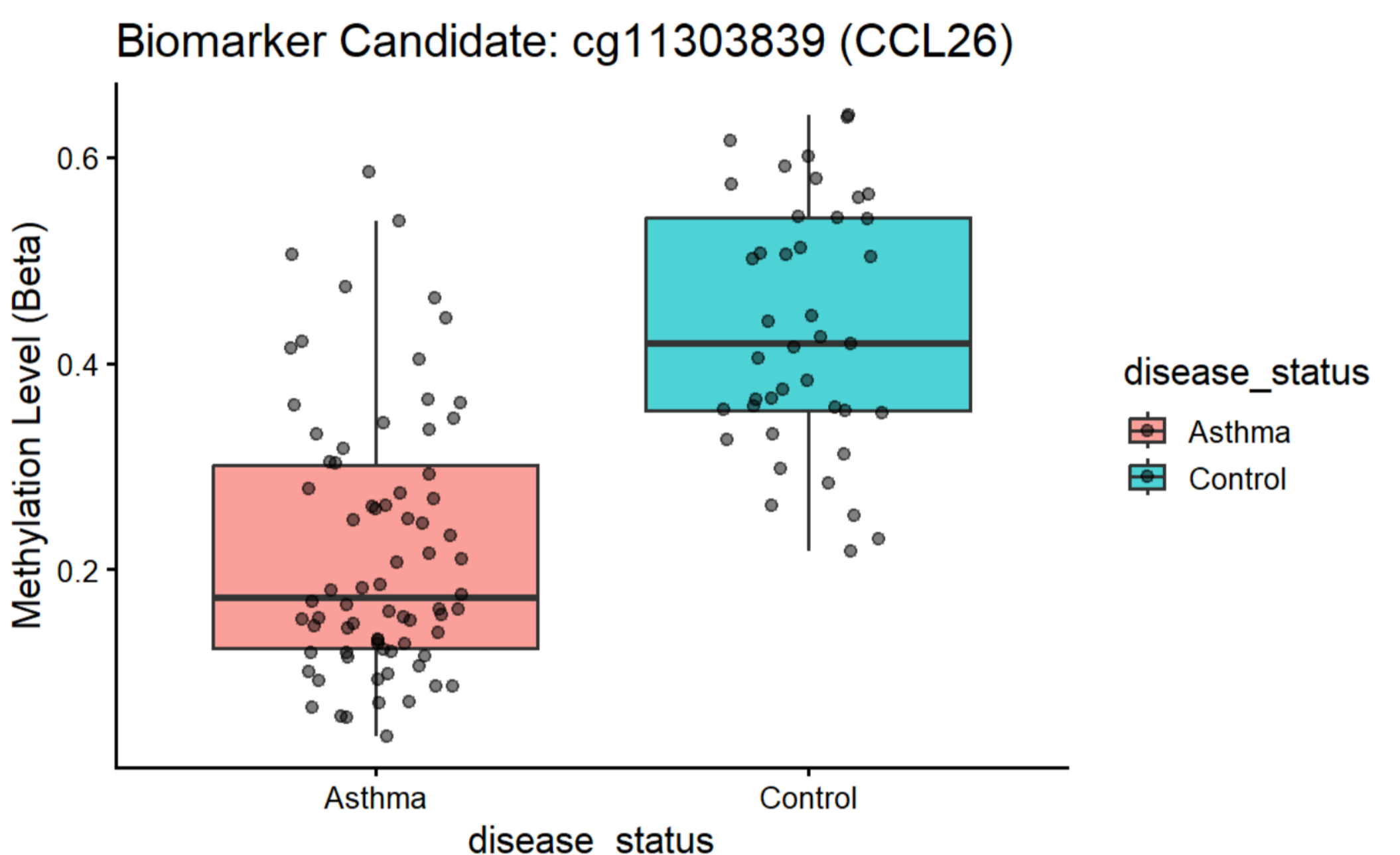
Divergent Enrichment Between Methylation and Gene Expression

- Methylation was enriched for developmental and morphogenetic pathways, suggesting reactivation of embryonic-like programs in asthma.
- Gene expression was enriched for immediate functional pathways, including calcium-dependent vesicle fusion and mucus secretion.
- Together, methylation reflects long-term structural changes, while expression captures short-term secretory activity.



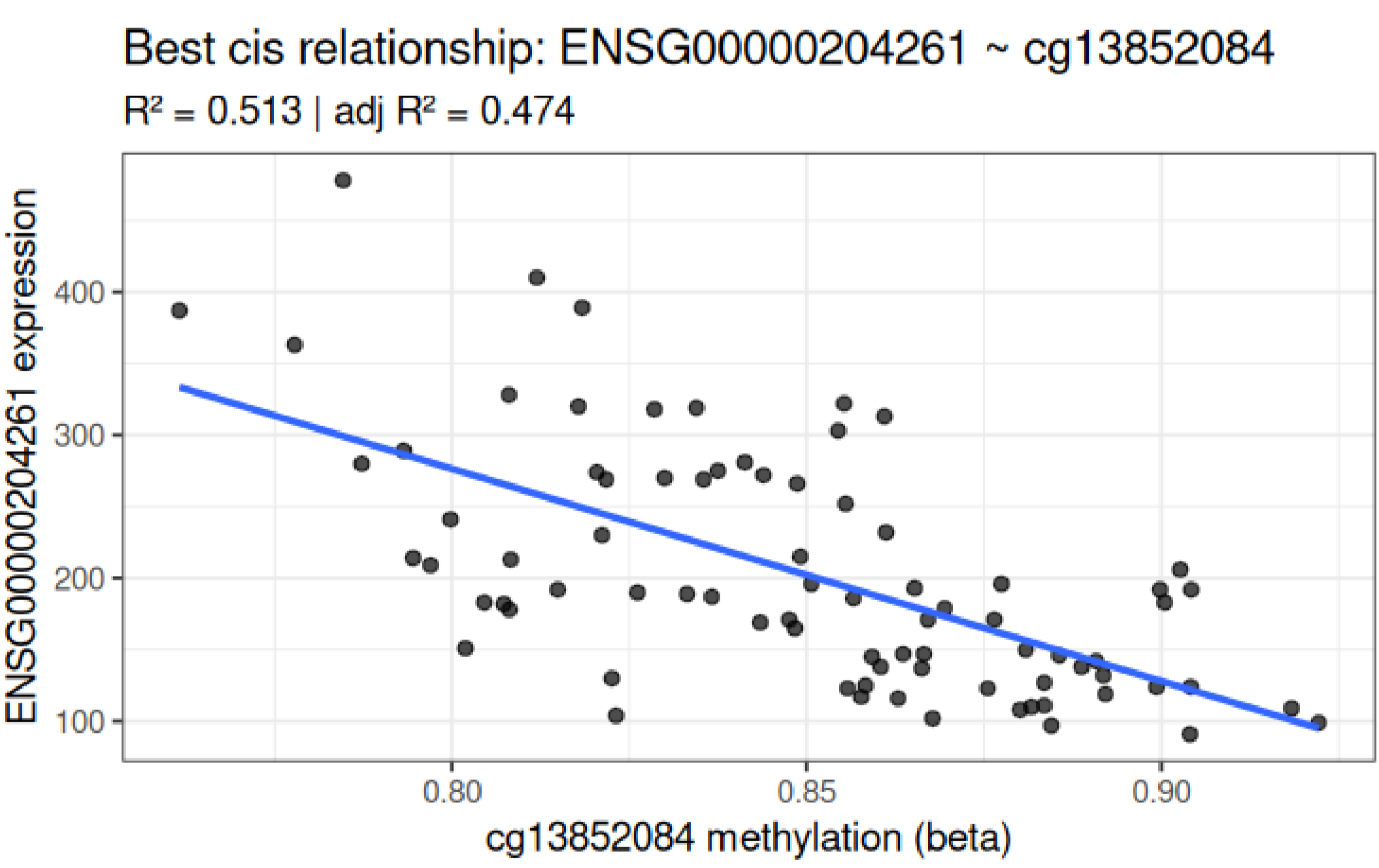
CCL26 Methylation Strongly Differentiates Asthma From Controls

- The cg11303839 CpG site in CCL26 shows significantly lower methylation in asthma compared to controls.
- This biomarker demonstrates high classification performance (AUC > 0.88), indicating its strong potential for asthma detection.



Local Methylation–Expression Coupling

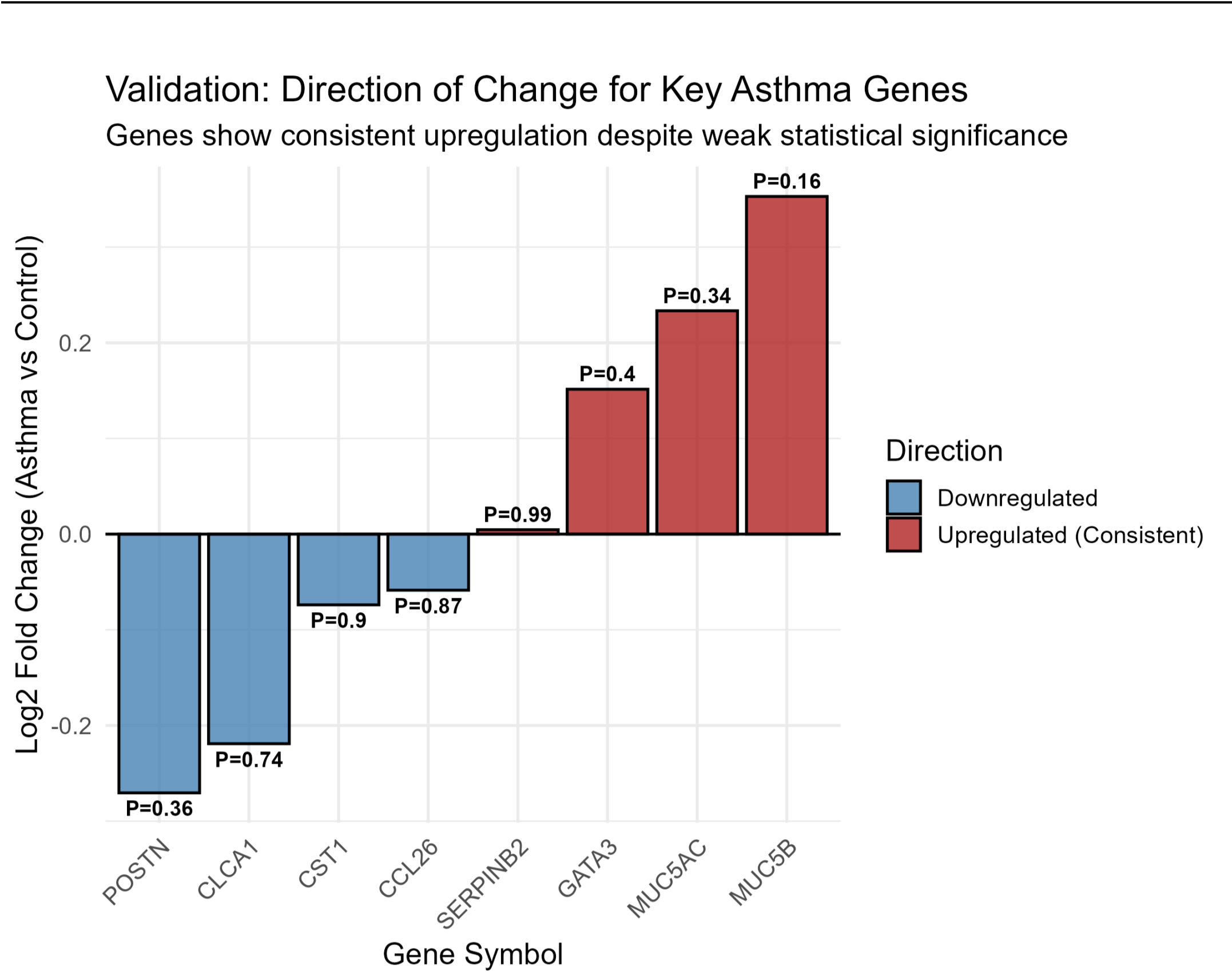
- Local (cis) CpG sites showed much stronger regulatory influence on gene expression than global methylation patterns.
- For many asthma-implicated genes, a single CpG explained 20--50% of expression variance.
- Here we show correlation observed for ENSG00000204261, where methylation at cg13852084 showed a robust negative correlation with expression ($R^2 \approx 0.51$).



Strongest cis methylation–expression relationship: expression of ENSG00000204261 versus methylation at cg13852084.

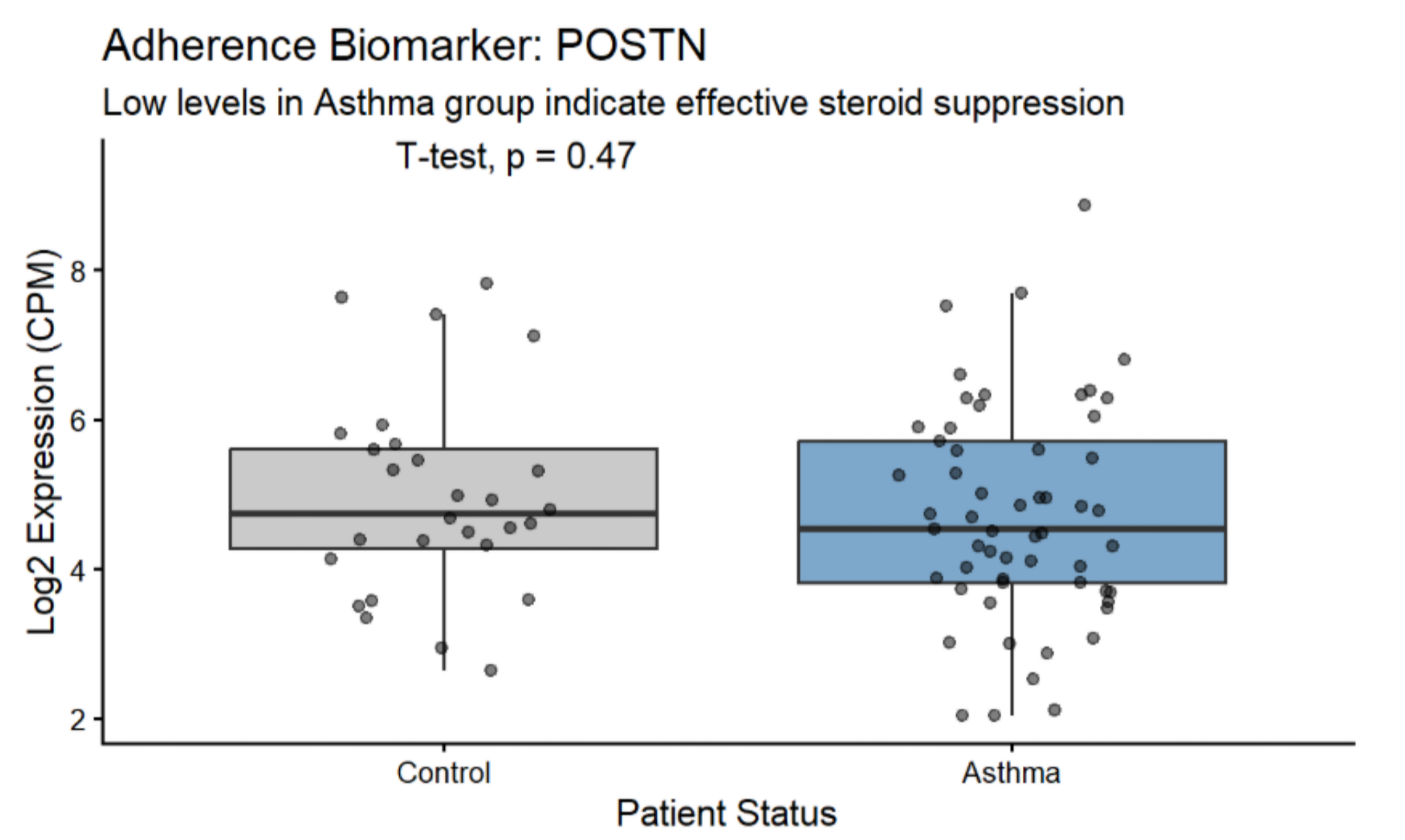
Unusual Gene Signatures due to corticosteroids

- Commonly upregulated inflammation associated genes were found to have a downregulating trend, while mucus associated genes had upregulating trend between cases and controls.
- This suggests that corticosteroids helped suppress inflammation but were not effective against mucus secretions.



POSTN Expression is Normalized by Corticosteroid Use

- Unlike typical asthma studies, POSTN expression levels show no clear difference between cases and controls.
- This suggests that corticosteroids effectively suppress type-2 inflammatory signals, making POSTN less reliable as a biomarker in treated adult asthma.



Exploratory Insights from Ingenuity Pathway Analysis (IPA)

- IPA was used as an exploratory tool to uncover pathways and key regulators linked to the differentially expressed genes.
- The results suggest ongoing immune-driven epithelial remodeling in asthma, pointing to possible mechanisms not fully corrected by treatment.
- These findings generate hypotheses for future work and highlight potential therapeutic targets.

