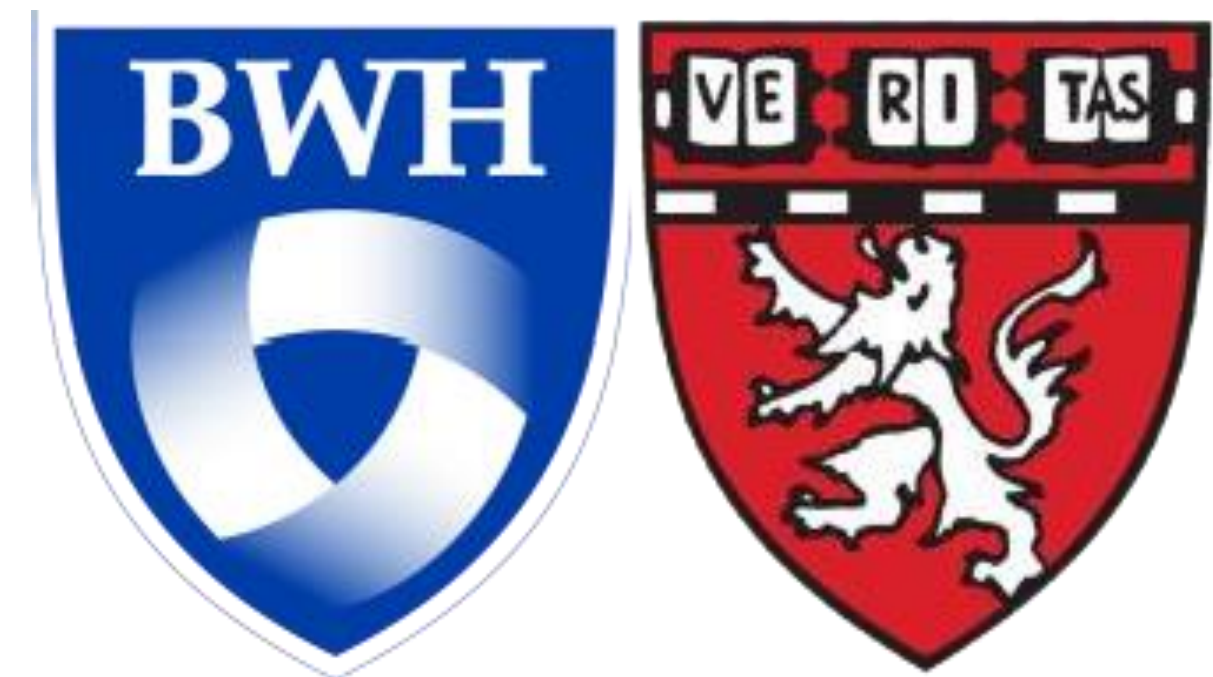


miRNA -Metabolome - Wide Association Study: A Multi-Omics Integrative Approach to Asthma

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INTRODUCTION

Both microRNAs (miRNAs) and metabolites have been identified as significant biomarkers for many conditions. Multiple studies have shown that various metabolic stimuli alter miRNA expression. Conversely, miRNAs regulate most cellular processes, impacting metabolism. We postulated that a systems integration of serum miRNAs and metabolites in a large childhood cohort could shed light on the combined synchronized role of miRNAs and metabolites in asthma and in broader metabolomic regulation.

METHODS

1121 serum samples from the Genetic Epidemiology of Asthma in Costa Rica Study (GACRS)

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miRNA Sequencing
targeted LC-MS metabolomic profiling

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- miRNAome-metabolome-wide association (miR-metabo-WAS) analysis using a generalized linear model with adjustment for age, gender, height, and BMI
- WGCNA (weighted co-expression network analysis) to identify clusters (modules) of metabolites significantly correlated with miRNA modules and clinical features of asthma.

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Replication and validation in CAMP cohort

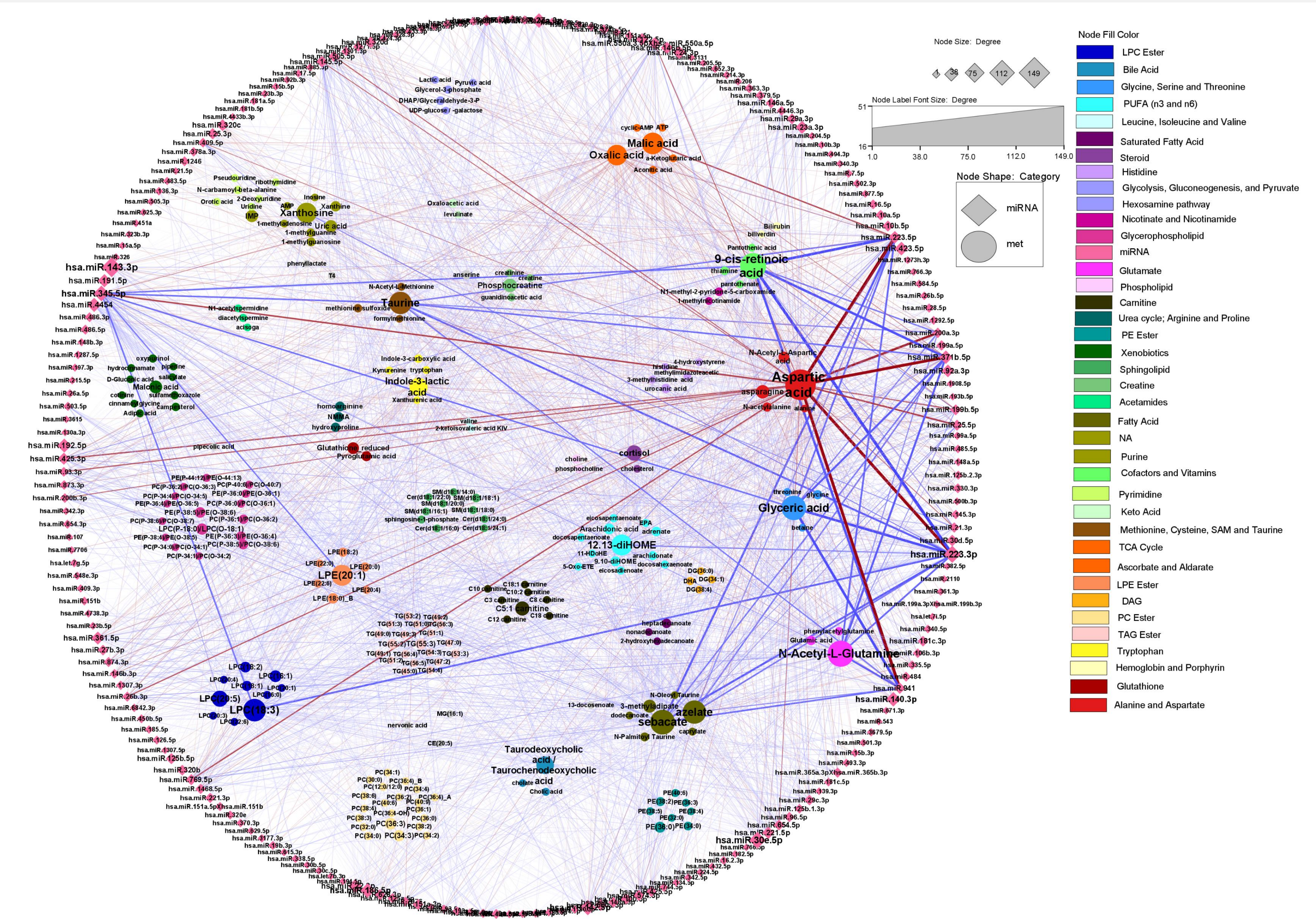


Figure 1. miRNAome-metabolome-wide association (miR-metabo-WAS) analysis: 2800 significant association between 214 miRNAs and 228 metabolites at 5% FDR. Edges [Red: positive beta-estimate Blue: negative beta-estimate] and weighted according to beta-estimate magnitude. Metabolites are grouped according to sub-pathways.

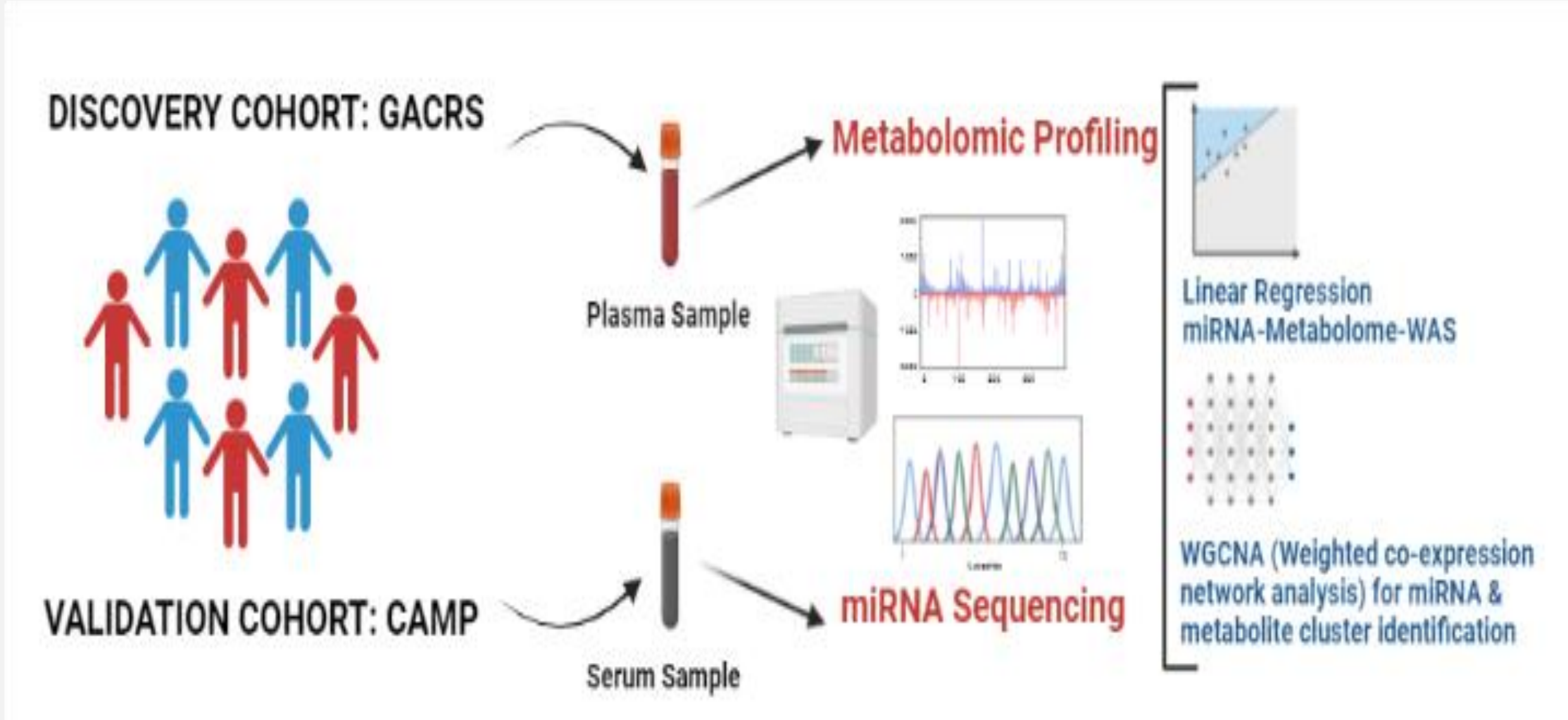


Figure 2. miRNAome-metabolome-wide association (miR-metabo-WAS) validation in CAMP cohort. 143 miRNA-metabolite association replicated in CAMP cohort; consist of 63 miRNAs and 30 metabolites.

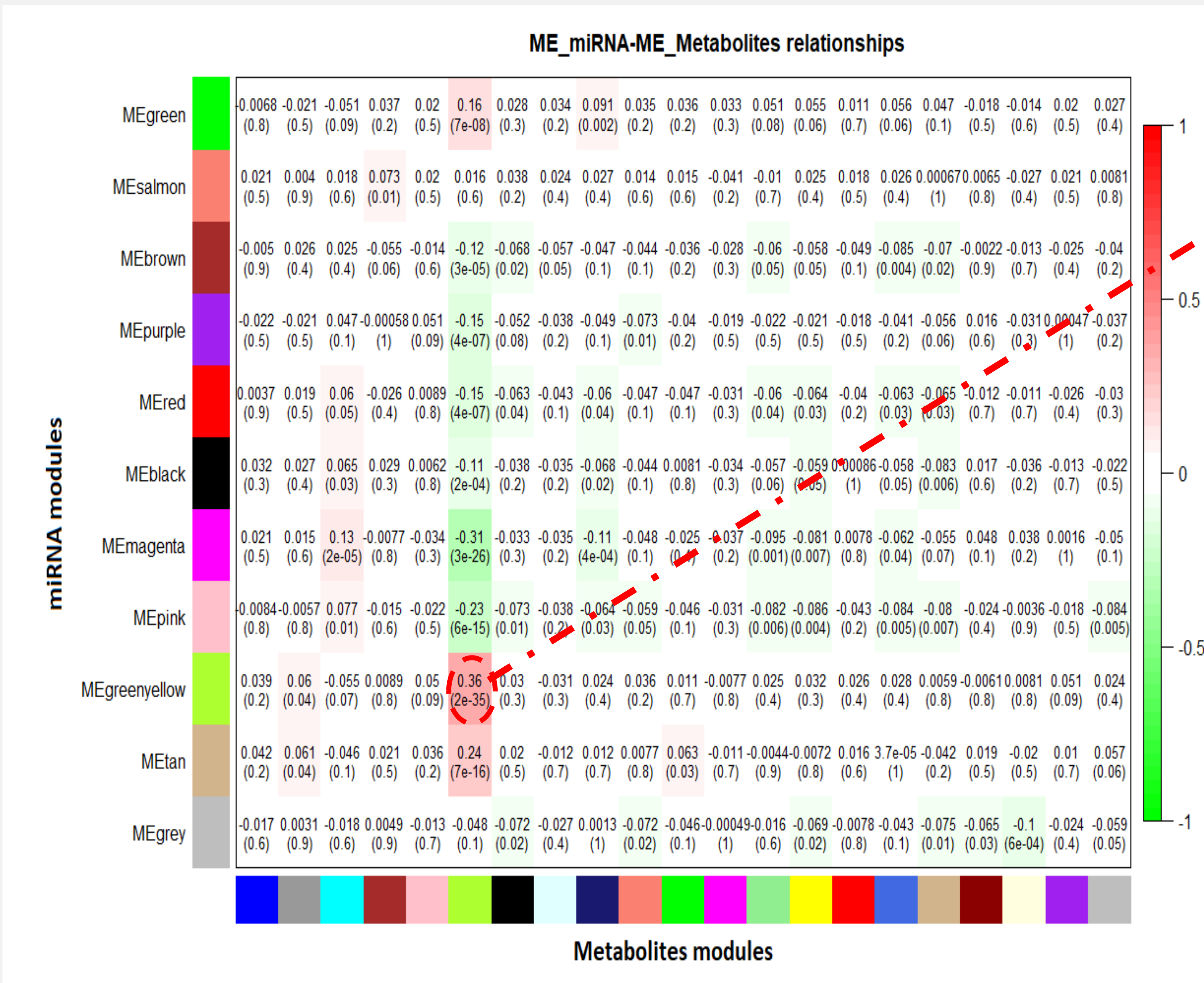


Figure 3. Relationships of miRNA module eigengenes and metabolite module eigengenes. Each row in the table corresponds to a miRNA module, and each column to a metabolite module. Numbers in the table report the correlations of the corresponding miRNA module eigengenes and metabolite module eigengenes, with the p-values printed below the correlations in parentheses. The table is color coded by correlation according to the color legend.

- ✓ 20 metabolites, including diHOME’s, sebacate, taurine, and cortisol, that were strongly correlated with six serum miRNAs (mir-143-3p, mir-22-3p, mir-320b/c/d and mir-483-5p).
- ✓ miRNAs and metabolite modules were associated with **airway hyper-responsiveness, airflow obstruction, forced expiratory volume in 1 second, eosinophil count and serum IgE, and asthma-related hospitalizations.**

Table 1. Module and clinical features association analysis result

Module	Term	P.Value	FDR
greenyellow	Forced expiratory volume in 1 second	5.89E-16	2.75E-14
greenyellow	Airway hyper-responsiveness	2.74E-09	2.88E-07
greenyellow	Eosinophil count	1.83E-06	3.85E-05
greenyellow	FEF25-75	1.66E-04	2.48E-03

CONCLUSION

The relatively concentrated effect of miRNAs on metabolite clusters shows that while miRNAs may target and regulate hundreds or thousands of genes, their impact on the resulting metabolome is fairly constrained in asthma. This study of serum miRNA and metabolites demonstrates the value of a combined microRNA-Seq and metabolomics approach to identify meaningful clinical associations and broader genomic regulation of cellular metabolism in Asthma.

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