Metabolomic Analyses of Asthma Phenotypes across Multiple Cohorts

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PURPOSE

Childhood asthma is a chronic airway disease characterized by traits of airway hyperresponsiveness, lung function, eosinophil counts, and atopy, amongst others.

As a disease with distinct heterogeneity, the identification of metabolites that are relevant broadly across a spectrum of disease phenotypes and specifically for particular disease characteristics, will likely prove important in the development of more personalized approaches to treatment.

Aim: To identify metabolites associated both broadly across and specifically with asthma phenotypes.

METHODS

Cohorts: Childhood Asthma Management Program (CAMP) Clinical Trial (n = 911) and the Genetic Epidemiology of the Costa Rica Cohort (GACRS) (n = 1,151).

Phenotypes: Airway hyperresponsiveness (methacholine challenge test - PC_{20}, PD_{20}); lung function (FEV_1, FEV_1/FVC, FEF_{25-75}, FEF_{25-75}/FVC); eosinophil count ($\log_{10}$(EOS)); and atopy ($\log_{10}$(IgE), skin prick test (positive count));

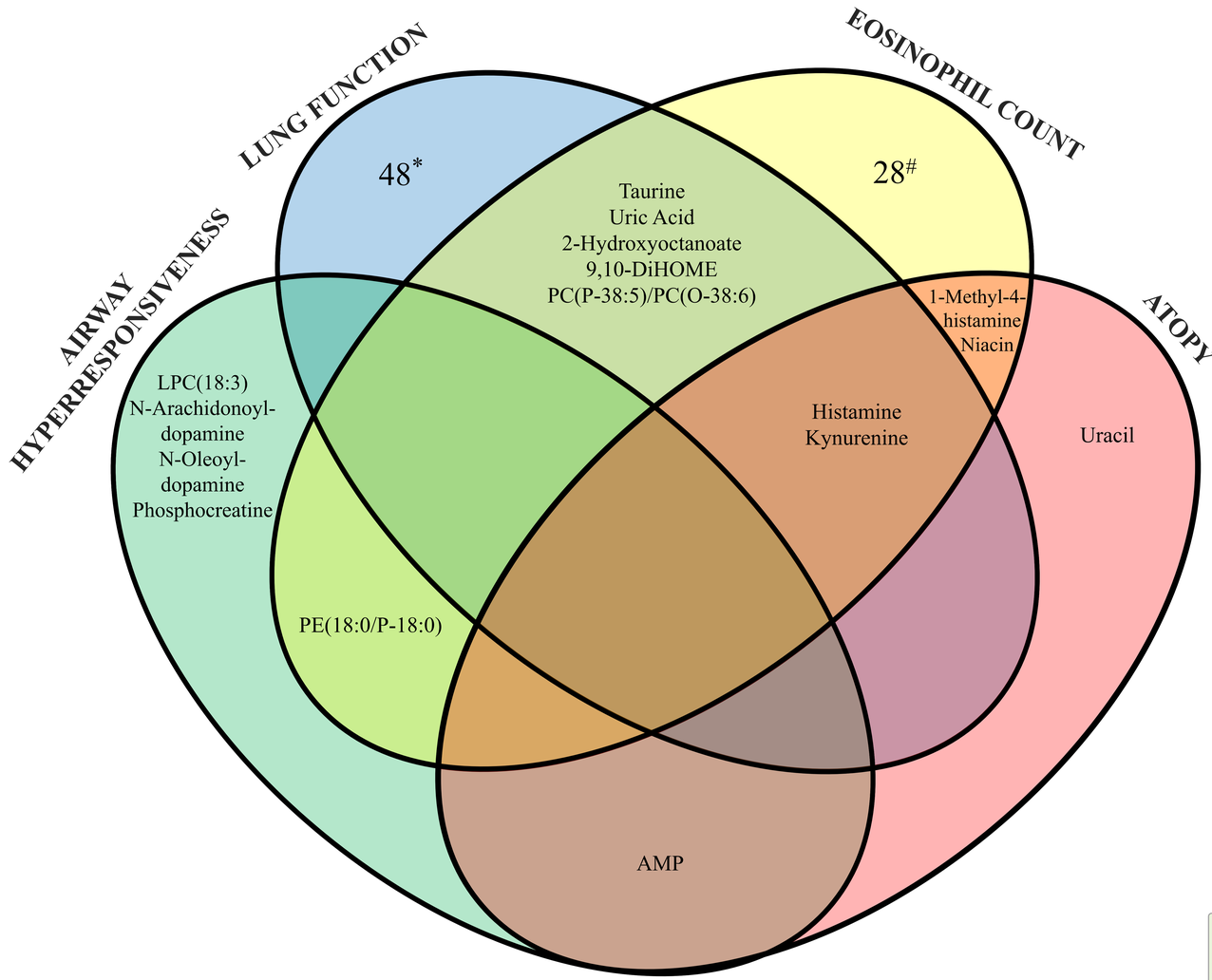
Metabolomics: Performed through the Broad Institute with 3 non-targeted platforms (C8 positive, C18 negative, HILIC positive), and 1 targeted platform (amide negative).

Statistical Analysis: Meta-analysis using Stouffer's Z-score method, adjusted for age, gender, BMI, and race. Significance was based on a $\text{Q-Value}_{\text{Meta}} < 0.05$, with the same direction of effect and P-Value < 0.10 for both CAMP and GACRS.

CONCLUSION

Using a meta-analysis approach, we identified various metabolites that were associated both broadly across and specifically with the measured asthma phenotypes. For example, histamine and kynurenine levels were significantly associated with increased eosinophil count, higher levels of atopy, and worse lung function.

RESULTS

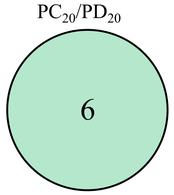


#
ADP
ATP
Bilirubin
Biliverdin
C16 Carnitine
C18:1 Carnitine
C18:2 Carnitine
LPC(20:5)
Metronidazole
Nudifloramide
PC(36:2)
PC(36:2)
PC(36:3)
PC(36:4)
PC(38:2)
PC(38:3)
PC(P-36:0)/PC(O-36:1)
PC(P-36:1)/PC(O-36:2)
PC(P-38:3)/PC(O-38:4)
PE(P-44:12)/PE(O-44:13)
Tauromuricholate
TG(52:2)
TG(54:2)
TG(54:3)
TG(55:2)
TG(55:3)
TG(56:3)
Tryptophan

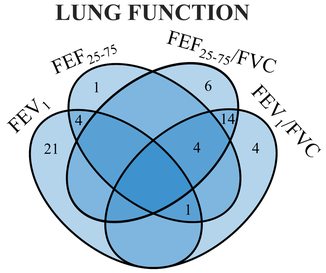
*
12.13-DiHOME
2-Aminoadipic Acid
2-Aminohippuric Acid
2-Ketoisovaleric Acid
7-dehydro-desmosterol
9-cis-Retinoic Acid
Arachidonic Acid
Asparagine
C5:1 Carnitine
C18 Carnitine
Campesterol
CE(16:1)
Cholesterol
Choline
Cortisol
Creatinine
Formylmethionine
GABA
Glyceric Acid
Glycocholate
Glycoursodeoxycholate
Glyoxylic Acid
Hydroxymyristate
Hydroxyproline
Indoleacetate
Kynurenic Acid
Methionine
N-Arachidonoyl Taurine
Ornithine
PC(34:3)
PC(P-34:0)/PC(O-34:1)
PE(P-36:3)/PE(O-36:4)
Phenylacetylglutamine
Proline
Pyroglutamic Acid
SM(d18:1/16:0)
SM(d18:1/16:1)
SM(d18:1/20:0)
SM(d18:1/22:0)
SM(d18:1/22:1)
SM(d18:1/24:0)
SM(d18:1/24:1)
Sphingosine-1-phosphate
Thyroxine
Taurochenodeoxycholate
Taurodeoxycholic Acid
Trimethylamine-N-oxide
Xanthosine

AIRWAY HYPERRESPONSIVENESS

PC_{20}/PD_{20}

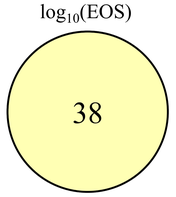


LUNG FUNCTION



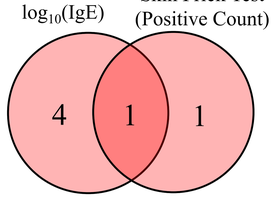
EOSINOPHIL COUNT

$\log_{10}$(EOS)



ATOPY

$\log_{10}$(IgE) Skin Prick Test (Positive Count)



AIRWAY HYPERRESPONSIVENESS

LUNG FUNCTION

EOSINOPHIL COUNT

ATOPY