

RESEARCH ARTICLE

Iron Status is Associated with Asthma and Lung Function in US Women

Emily P. Brigham¹, Meredith C. McCormack^{1,2}, Clifford M. Takemoto³, Elizabeth C. Matsui^{2,4*}

1 Johns Hopkins University School of Medicine, Division of Pulmonary and Critical Care Medicine, Baltimore, Maryland, United States of America, **2** Johns Hopkins University Bloomberg School of Public Health, Baltimore, Maryland, United States of America, **3** Johns Hopkins University School of Medicine, Division of Pediatric Hematology, Baltimore, Maryland, United States of America, **4** Johns Hopkins University School of Medicine, Division of Pediatric Allergy and Immunology, Baltimore, Maryland, United States of America

* ematsui@jhmi.edu



Abstract

Background

Asthma and iron deficiency are common conditions. Whether iron status affects the risk of asthma is unclear.

Objective

To determine the relationship between iron status and asthma, lung function, and pulmonary inflammation.

Methods

Relationships between measures of iron status (serum ferritin, serum soluble transferrin receptor (sTfR), and sTfR/log10ferritin (sTfR-F Index)) and asthma, lung function, and pulmonary inflammation were examined in women 20–49 years in the National Health and Nutrition Examination Survey. Logistic, linear, and quadratic regression models accounting for the survey design of NHANES were used to evaluate associations between iron status and asthma-related outcomes and were adjusted for race/ethnicity, age, smoking status, income, and BMI.

Results

Approximately 16% reported a lifetime history of asthma, 9% reported current asthma, and 5% reported a recent asthma episode/attack ($n = 2906$). Increased ferritin (iron stores) was associated with decreased odds of lifetime asthma, current asthma, and asthma attacks/episodes in the range of ferritin linearly correlated with iron stores (20–300 ng/ml). The highest quintile of ferritin (>76 ng/ml) was also associated with a decreased odds of asthma. Ferritin levels were not associated with FEV1. Increased values of the sTfR-F Index and sTfR, indicating *lower* body iron and *higher* tissue iron need, respectively, were associated with decreased FEV1, but neither was associated with asthma. None of the iron indices were associated with FeNO.

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Conclusion

In US women, higher *iron stores* were inversely associated with asthma and lower *body iron* and higher *tissue iron need* were associated with lower lung function. Together, these findings suggest that iron status may play a role in asthma and lung function in US women.

Introduction

Asthma is one of the most common diseases in the United States. One in 11 children and 1 in 12 adults have asthma, and this disease resulted in 10.5 million missed school days and 14.2 million missed work days in 2008. The United States spends \$56 billion annually on asthma medications [1]. Iron deficiency is also one of the most common nutritional deficiencies in the US [2,3] and is thought to be more prevalent in populations at greatest risk for asthma [3,4], suggesting that these two conditions may be linked.

While the role that iron plays in asthma is unknown, a physiologic link to asthma and inflammatory diseases like asthma has been suggested in animal models. A low iron diet resulted in pronounced asthma in a mouse model of allergic asthma, and this effect appeared to be mediated by increased mast cell reactivity in the setting of low iron [5]. Because these observations suggest that poor iron status could promote asthma, we hypothesized that lower iron would be associated with a greater risk of asthma, greater pulmonary inflammation, and decreased lung function. To test this hypothesis, we used iron indices and asthma data collected from women participating in the National Health and Nutrition Survey (NHANES) from 2007–2010.

Methods

Study Population

NHANES is a recurring survey of the non-institutionalized civilian US population (http://www.cdc.gov/nchs/nhanes/nhanes_questionnaires.htm). For this analysis, data from the 2007–2008 and 2009–2010 surveys were used because these years captured measures of iron status, lung function, and exhaled nitric oxide, as well as asthma outcomes. These data were only captured by NHANES in females 12–49 years of age. Because smoking status, a potentially important confounder, was best characterized in participants 20 years and older, our primary analysis was limited to adult females, ages 20–49 years. Therefore our primary sample is representative of the United States female, civilian, non-institutionalized population ages 20–49 years.

Iron Indices

Serum ferritin, a measure of *iron stores*, was measured via the Roche/Hitachi 912 immunoturbidimetric assay in 2007–2008 and the Roche Elecsys 170 (E170) sandwich immunoassay in 2009–2010. In order to combine ferritin data that were measured using two different assays, the 2009–10 ferritin values were converted to values equivalent to the 2007–8 values using a publicly available equation derived from a Deming regression analysis [6]. Since ferritin has some inherent limitations as a measure of iron stores [7,8], relationships between ferritin and asthma-related outcomes were examined both across the full range of ferritin and within the range of ferritin that is most strongly and linearly correlated with iron stores (20–300 ng/ml) [9–12].

Serum transferrin receptor (sTfR), which is a measure of *tissue iron need* [13], was also measured in NHANES. sTfR was measured via the Roche Hitachi 912 immunoturbidimetric assay

in 2007–2008 and the Roche Hitachi Mod P immunoturbidimetric method in 2009–2010. If values of either ferritin or serum transferrin receptor were below the limit of detection, values were assigned as the lower limit of detection divided by the square root of two. A sTfR-F Index, which estimates *total body iron*, was calculated with the following equation, as previously reported [14]: $sTfR/\log_{10}(\text{ferritin})$. Increasing levels indicate increasing iron insufficiency.

Asthma and Lung Function

To assess asthma prevalence, participants were asked whether a physician had ever diagnosed them with asthma, whether they still had asthma, and whether they had an asthma attack or episode within the prior year.

Spirometry was conducted in eligible participants, which were those without a prohibitive medical condition (current chest pain, physical problem with forced expiration, supplemental oxygen, recent eye, chest, or abdominal surgery, recent heart attack, stroke, tuberculosis exposure or coughing up blood, history of detached retina or collapsed lung). Quality attributes were assigned to each FEV₁ and FVC, and those that were reported as “questionable” or “results not valid” were excluded from the analysis. No quality attributes specific to the FEF 25–75% were available, and all values were included. Percent predicted values were calculated using Hankinson et al. (1999) prediction equations [15].

Fractional exhaled nitric oxide (FeNO) was measured with the Aerocrine NIOX MINO[®] (Aerocrine AB, Solna, Sweden) in eligible participants, which were those without a prohibitive medical condition (current chest pain, a physical problem with forceful expiration, using supplementary oxygen). The mean of two reproducible measurements was used for analysis. A reproducible measurement was defined as either below 30 ppb and within 2ppb of each other, or above 30 ppb and within 10% of each other. Two data points that were below the limit of detection were assigned a value of 3.5ppb, which is the lower limit of normal detection divided by the square root of 2. Two data points that were above the upper limit of detection (300ppb) were assigned a value of 301ppb.

Statistical Analyses

All analyses used survey methods to account for the sampling scheme in NHANES and produce estimates representative of women ages 20–49 years in the US population. Ferritin and transferrin receptor concentrations, sTfR-F Index, as well as FeNO results, were log₁₀-transformed. Linear and logistic regression analyses were performed to examine associations between measures of iron status and lung function, FeNO, and asthma. Potential confounders thought to be associated with iron status and asthma were included in multivariable models and included age, race/ethnicity, smoking status, income, and body mass index (BMI). Ferritin was examined: (1) across its full range, (2) in the range linearly correlated with iron stores (20–300 ng/ml inclusive), and (3) as quintiles. The quintile analyses were performed to explore the linearity of the relationships between ferritin and the outcomes of interest. Exploratory analyses suggested non-linear relationships between the full range of ferritin and some of the outcomes, therefore quadratic regression models were also applied. Sensitivity analyses were conducted by removing subjects with evidence of inflammation, which can elevate serum ferritin levels (defined as a total white blood cell count >10,000 cells/mm³ or C-reactive protein > 6.0 mg/dl) [16]. In addition, we investigated the combined effects of anemia and iron-deficiency on the outcomes of interest by categorizing anemia as a hemoglobin ≤12.0 g/dl (per World Health Organization Program Guidelines [17]) and iron deficiency as ferritin <20 ng/ml. All analyses were conducted with Stata SE (Version 11.2, StataCorp, College Station, TX). A two-tailed p-value <0.05 was considered statistically significant.

Results

Study Population Characteristics

The sample population was composed of females 20–49 years of age who participated in NHANES between 2007 and 2010. Survey-weighted characteristics therefore reflect the characteristics of non-institutionalized females 20–49 years in the US during this time period ([Table 1](#), $n = 2906$). Approximately 16% of this US subpopulation ever had asthma, 9.1% had current asthma, and 5% had an asthma attack in the past year. Mean values for lung function indices and pulmonary inflammation, as captured by FeNO, were all within normal limits, as expected for a US population-based sample. The mean ferritin, an indicator of *iron stores*, was 36.4 ng/ml (SD: 0.7) and the mean sTfR, an indicator of *tissue iron need*, was 3.1 mg/L (SD: 0.03). Just under 25% had a ferritin less than 20 ng/mL, suggestive of deficient iron stores [[18–20](#)]. Cut points for quintiles of ferritin (ng/ml) as follows: Q1: 1.8–15.7; Q2: 16.0–28.7; Q3: 29.0–46.6; Q4: 47.0–76.0; and Q5: 76.8–1051.2. Within the fifth quintile, only 3% of values were above 300 ng/ml.

Relationships Between Iron Status and Asthma

Because ferritin is linearly correlated with iron stores in the range from 20–300 ng/ml, relationships between ferritin and asthma were examined in this range of ferritin. Models restricted to the range linearly related to iron stores (20–300 ng/ml) were created, and indicated that a ten-fold increase in ferritin within this range was associated with a 39% decrease in the odds of lifetime asthma (OR [95% CI]: 0.61 [0.39 to 0.95]), a 53% decrease in the odds of current asthma (OR [95% CI]: 0.47 [0.27 to 0.81]) and a 62% decrease in the odds of an asthma attack in the past year (OR [95% CI]: 0.38 [0.17 to 0.86]) adjusted for race/ethnicity, age, smoking, income, and BMI.

Analyses of relationships between ferritin quintiles created using the entire range of ferritin values and asthma demonstrated significantly decreased odds of all asthma outcomes for those in the highest ferritin quintile (>76 ng/ml) compared to those in the lowest four quintiles (1.8–76 ng/ml) ([Table 2](#)). Results of analyses showing relationships between each ferritin quintile and asthma outcomes are available in [S1 Table](#). Sensitivity analyses excluding the lowest quintile (ferritin <16.0 ng/ml, all iron deficient), and removing subjects with evidence of inflammation (defined as a total white blood cell count $>10,000$ cells/mm³ or C-reactive protein >6.0 mg/dl) did not appreciably affect results (data not shown).

Significant relationships between the entire range of ferritin and asthma were not evident in a linear prediction model ([Table 2](#)). However, there was evidence to support non-linear relationships between ferritin and asthma outcomes ([Fig. 1](#)). Quadratic models demonstrated significant, non-linear relationships between ferritin and lifetime and current asthma (quadratic term p -values <0.05) and a trend towards a non-linear relationship with asthma attack/episode in the past year (quadratic term p -value = 0.10) ([S2 Table](#)). Specifically, at levels of ferritin that reflect deficient iron stores (<20 – 30 ng/ml), the odds of lifetime and current asthma increased with increasing ferritin levels ([Fig. 1](#)). However, as ferritin levels increased from levels reflective of insufficient iron stores (<20 – 30 ng/ml) to levels reflective of sufficient iron stores, the odds of these asthma outcomes decreased.

Neither sTfR (*tissue iron need*) nor the sTfR-F Index (*total body iron*) were associated with the asthma outcomes. Results are shown in [Table 2](#).

Relationships Between Iron Status and Lung Function and Pulmonary Inflammation

Ten-fold increases in sTfR (*tissue iron need*) or the sTfR-F Index (*total body iron*) were associated with a significant decrease in FEV₁ percent predicted (β coefficient [95% CI]: -4.5 [-8.2 to -0.8])

Table 1. Population characteristics (n = 2906).

Socio-demographic Characteristics	
Age (years)	35.0 (0.2)
Race/Ethnicity, % (SE)	
Non-Hispanic white	63.3 (3.0)
Non-Hispanic black	12.9 (1.3)
Mexican American	9.9 (1.4)
Other race or multiracial	7.3 (1.0)
Other Hispanic	6.5 (1.1)
Income to poverty ratio [§]	2.8 (0.07)
Smoking status, % (SE)	
Current	23.7 (1.4)
Former	14.3 (0.8)
Never	62.0 (1.9)
Asthma	
Lifetime, % (SE)	16.1 (0.9)
Current, % (SE)	9.1 (0.7)
Attack/Episode in Past Year, % (SE)	5.0 (0.5)
Pulmonary Function/Inflammation	
FEV ₁ [†]	
Actual value (ml)	3027.2 (16.1)
% predicted	98.5 (0.4)
FVC [§]	
Actual value (ml)	3739.1 (18.5)
% predicted	101.3 (0.3)
FEF _{25/75} [‡]	
Actual value (ml/s)	3109.2 (26.0)
% predicted	94.1 (0.7)
FEV ₁ /FVC ratio [§]	0.81 (0.002)
eNO (ppb) [¶]	11.4 (0.3)
Measures of Iron Status	
Ferritin (ng/ml)	36.4 (0.7)
Soluble transferrin receptor (mg/L) ^λ	3.1 (0.03)
sTfR/log ₁₀ (ferritin) ^λ	2.1 (0.02)
Iron deficient, * % (SE)	23.3 (0.8)

All data posted as mean (SE) unless otherwise indicated. Geometric means are presented for all variables log-transformed in presented analyses.

*ferritin < 20ng/ml

SE = linearized standard error

[§]n = 2678;

[†]n = 2415;

[§]n = 2378;

[‡]n = 2444;

[§]n = 2374;

[¶]n = 2470;

^λn = 2901

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Table 2. Relationships between iron status and asthma outcomes.

	Lifetime Asthma		Current Asthma		Asthma Attack/Episode in Past Year	
	Unadjusted	Adjusted* OR (95% CI)	Unadjusted	Adjusted* OR (95% CI)	Unadjusted	Adjusted* OR (95% CI)
Ferritin Iron Indices (higher levels indicative of more iron)						
Log ₁₀ (ferritin) [‡]	0.89 (0.69 to 1.16)	0.81 (0.64 to 1.04)	0.90 (0.66 to 1.23)	0.78 (0.57 to 1.04)	1.03 (0.74 to 1.45)	0.84 (0.65 to 1.09)
Log ₁₀ (ferritin) [§] _(20–300 ng/ml)	0.61 (0.39 to 0.94)	0.61 (0.39 to 0.95)	0.59 (0.36 to 0.97)	0.47 (0.27 to 0.81)	0.65 (0.30 to 1.42)	0.38 (0.17 to 0.86)
Ferritin, quintile 5 vs. quintiles 1–4 [‡]	0.77 (0.58 to 1.02)	0.69 (0.52 to 0.91)	0.84 (0.61 to 1.15)	0.64 (0.45 to 0.92)	0.85 (0.55 to 1.32)	0.56 (0.38 to 0.84)
Serum Transferrin Receptor Iron Indices (higher levels indicative of less iron)						
Log ₁₀ (sTfR) [‡]	1.36 (0.83 to 2.21)	1.30 (0.76 to 2.21)	1.61 (0.73 to 3.58)	1.15 (0.46 to 2.85)	2.13 (0.73 to 6.18)	1.67 (0.47 to 5.98)
Log ₁₀ (sTfR/log ₁₀ ferritin) [‡]	1.14 (0.82 to 1.58)	1.20 (0.86 to 1.66)	1.22 (0.76 to 1.95)	1.18 (0.72 to 1.92)	1.26 (0.71 to 2.25)	1.27 (0.69 to 2.37)

*Adjusted for race/ethnicity, age, smoking, income, and BMI

Bolded results are statistically significant, with $p < 0.05$

[‡]n = 2906 for unadjusted, n = 2663 for adjusted; ferritin Q1–4: 1.8–76.0ng/ml, Q5: >76.0ng/ml

[§]Ferritin restricted to values from 20 to 300 ng/ml, inclusive; n = 2134 for unadjusted, n = 1963 for adjusted

[†]n = 2901 for unadjusted, n = 2658 for adjusted

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and -2.1 [-4.2 to -0.1], respectively) (Table 3). Increases in both sTfR (*tissue iron need*) and the sTfR-F Index (*total body iron*) were also associated with significant decreases in FEF 25–75 percent predicted (β coefficient [95% CI]: -8.5 [-14.5 to -2.4] and -5.1 [-8.7 to -1.4], respectively). These relationships were consistently present in models using actual rather than percent predicted spirometric values (S3 Table). Neither sTfR (*tissue iron need*) nor the sTfR-F Index (*total body iron*) was associated with FeNO levels.

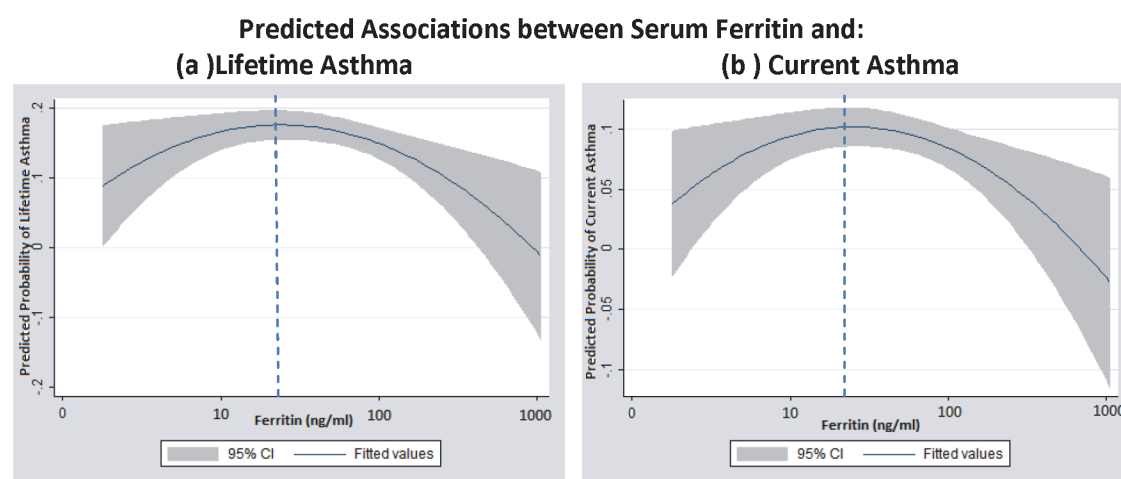


Fig 1. Predicted relationships between the full range of ferritin concentrations and asthma-related outcomes, generated from regression models: (a) lifetime asthma and (b) current asthma. 95% confidence intervals are depicted by the shaded areas. Vertical line represents approximately 20ng/ml ferritin.

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Table 3. Relationships between iron status and lung function and FeNO.

	FEV ₁ /FVC ratio β (95% CI)	FEV ₁ % predicted β (95% CI)	FVC % predicted β (95% CI)	FEF 25–75% predicted β (95% CI)	Log ₁₀ (FeNO) β (95% CI)
Ferritin Iron Indices (higher levels indicative of more iron)					
Log ₁₀ (ferritin) [‡]	0.009 (0.003 to 0.01)	0.2 (-1.0 to 1.4)	-0.8 (-2.0 to 0.4)	2.5 (-0.03 to 5.1)	-0.01 (-0.05 to 0.03)
Log ₁₀ (ferritin) [§] _(20–300 ng/ml)	0.01 (0.004 to 0.03)	-1.9 (-4.8 to 0.9)	-3.4 (-6.4 to -0.3)	3.5 (-1.3 to 8.3)	-0.05 (-0.1 to 0.01)
Ferritin, quintile 5 vs. quintiles 1–4 [‡]	0.01 (0.002 to 0.02)	-0.1 (-1.5 to 1.3)	-1.1 (-2.7 to 0.5)	2.4 (-0.7 to 5.6)	-0.03 (-0.06 to 0.004)
Serum Transferrin Receptor Iron Indices (higher levels indicative of less iron)					
Log ₁₀ (sTfR) [†]	-0.02 (-0.04 to 0.0008)	-4.5 (-8.2 to -0.8)	-2.6 (-7.1 to 1.8)	-8.5 (-14.5 to -2.4)	0.03 (-0.05 to 0.11)
Log ₁₀ (sTfR/log ₁₀ ferritin) [†]	-0.01 (-0.02 to -0.002)	-2.1 (-4.2 to -0.1)	-0.8 (-3.2 to 1.7)	-5.1 (-8.7 to -1.4)	0.02 (-0.03 to 0.07)

Adjusted for race/ethnicity, age, smoking, income, and BMI

Bolded results are statistically significant, with $p < 0.05$

[‡]FEV₁/FVC % (n = 2198); FEV₁% predicted (n = 2236); FVC (n = 2201); FEF 25–75% predicted (n = 2261); Log₁₀(FeNO) (n = 2279); ferritin Q1–4: 1.8–76.0 ng/ml, Q5: >76.0 ng/ml

[§]Ferritin restricted to values from 20 to 300 ng/ml, inclusive; FEV₁/FVC % (n = 1630); FEV₁% predicted (n = 1657); FVC (n = 1633); FEF 25–75% predicted (n = 1676); Log₁₀(FeNO) (n = 1686)

[†]FEV₁/FVC % (n = 2195); FEV₁% predicted (n = 2233); FVC (n = 2198); FEF 25–75% predicted (n = 2258); Log₁₀(FeNO) (n = 2276)

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Overall, higher ferritin levels were not associated with better lung function or lower FeNO levels (Table 3; S4 and S5 Tables). Although ferritin across the full range was associated with a higher FEV₁/FVC ratio, this finding was explained by the association between higher ferritin levels and a lower FVC (Table 3). As expected, similar relationships were present in models using actual rather than percent predicted spirometric values (S3 Table).

Iron Deficiency, Anemia, and Asthma-related Outcomes

We examined the effects of iron deficiency with and without anemia on asthma, lung function, and pulmonary inflammation. There were no associations between iron deficiency with or without anemia and asthma outcomes, lung function, or pulmonary inflammation when comparing iron-sufficient, non-anemic individuals to any of the other categories (S6 and S7 Tables).

Secondary Analyses: Age 12–19

As a secondary analysis of the data available in NHANES, we examined the above relationships in adolescent females age 12–19. We found a significant, positive relationships between sTfR (*tissue iron need*) and asthma attack (OR [95% CI]: 6.13 [1.16 to 32.43]) and sTfR-F Index (*total body iron*) and asthma attack (OR [95% CI]: 2.97 [1.01 to 8.71]), consistent with the results in adult females (S8 Table). We did not observe any relationships between ferritin and asthma outcomes among adolescent females. However, it is important to note that the distribution of ferritin was lower in this younger age group than in the adult female population, as only 6.4% of adolescent females had a ferritin greater than 76 ng/ml, the level found to be protective in the adult population. Furthermore, sample size in adolescents (n = 1046) was roughly one third that of adults (n = 2906), so that statistical power was lower in the adolescent analyses than the adult women analyses. We did not find meaningful relationships between any of the iron indices and lung function in these analyses restricted to adolescent females (data not shown).

Discussion

We found that higher iron stores, as represented by higher serum ferritin, were associated with a lower prevalence of asthma in US women 20–49 years of age. Specifically, ferritin >76 ng/ml was associated with decreased odds of lifetime asthma, current asthma and asthma attack/episode in the past year. Notably, increases in tissue iron need and decreases in body iron, (represented by lower sTfR and lower sTfR-F Index, respectively) were linked to decreases in FEV₁, suggesting that tissue and body iron may influence lung function. Together, these findings suggest that iron status could have significant effects on pulmonary physiology and the risk of asthma. Given that suboptimal iron status and asthma are both common in the United States, a better understanding of the relationship between iron and asthma could provide an opportunity to intervene on asthma through iron supplementation.

While poor neurodevelopmental outcomes and cancer prognosis have been linked to iron deficiency, [21–23], links between iron status and pulmonary disease remain relatively unexplored. However, some recent studies suggest that iron status may affect the lungs. In one study, iron supplementation in iron deficient women (average serum ferritin of 9.3 ng/ml at baseline, increased to an average of 42.9 ng/ml after supplementation) led to resolution of chronic cough and bronchial hyperreactivity [24]. Notably, forty-one percent of these women had normal hemoglobin levels at baseline prior to supplementation, implicating iron repletion as the primary factor in their symptom improvement. In a study of children in India, anemia, which was predominantly due to iron deficiency, was associated with asthma [25]. Lastly, a birth cohort study found an inverse association between umbilical cord iron levels and later onset wheeze and eczema [26]. Iron deficiency has also been associated with poorer functional status in patients with idiopathic pulmonary hypertension (IPH) [27]. Because of this link between iron status and functional status in IPH and the observation that iron can decrease pulmonary arterial vasoconstriction [28,29], a clinical trial is planned to determine the effects of iron supplementation on IPH [30]. Together these studies lend credence to the general notion that iron status may have direct effects on the lungs, and are supportive of our findings demonstrating an association between iron status and asthma and lung function.

Our study's findings are further supported by *in vitro* and mouse models, which point to the potential biological basis of the association between iron status and asthma-related outcomes. For example, mouse model studies have demonstrated that iron administration reduces airway eosinophilia and hyperreactivity [5,31]. One of these studies also demonstrated less production of pro-inflammatory cytokines in male mice fed an iron sufficient diet compared to male mice fed an iron deficient diet, but who had not progressed to anemia [5]. Iron stores were five to six times and higher in the liver and spleen of mice fed an iron sufficient diet as compared to an iron deficient diet, indicating that the differences seen were associated with actual induced differences in iron stores. The highest increase in cytokine level was noted in IL-17, a known mediator for asthma in humans [32]. Furthermore, mast cells incubated in low iron media had an increase in IgE-mediated degranulation [5]. As mast cells and eosinophils play important roles in the acute and chronic inflammation of asthma, the studies above support the biologic plausibility of a causal relationship between iron status, asthma, and lung function [33–35].

In our study, there was a clear and consistent association between the highest ferritin quintile (>76ng/ml) and decreased odds of all three asthma outcomes, suggesting that supplementation with iron aimed at increasing ferritin to a level above this threshold could be an experimental target for asthma risk reduction. Interestingly, in other disease states affected by iron stores, a similar threshold effect of ferritin has been observed. In restless leg syndrome and alopecia, for example, iron supplementation to achieve ferritin levels of at least 50 ng/ml [36] and 70 ng/ml, respectively, have been proposed [37,38].

Ferritin levels, however, were not associated with better lung function, and instead were associated with a lower FVC. As lower FVC is a feature of restrictive lung disease, this finding merits further investigation in future studies. The other two iron indices, sTfR (*tissue iron need*) and the sTfR-F Index (*total body iron*), were not associated with asthma outcomes, but were associated with FEV₁ and FEF_{25–75}. Specifically, higher *tissue iron need* and lower *total body iron* were associated with a lower FEV₁ and a lower FEF_{25–75}, lung function findings that would be consistent with asthma, suggesting that iron status may influence lung function. Together, the associations between the iron indices and asthma and lung function support the hypothesis that iron may play a role in the initiation and/or perpetuation of asthma.

The nonlinear association between the full range of ferritin and asthma in our study is curious, but perhaps not without reason. For example, it is possible that at the low end of the ferritin/iron stores spectrum, those with frank iron deficiency are unable to mount a robust inflammatory response and therefore may be protected against asthma. As iron stores are repleted, immune cell function improves, the inflammatory response is restored, and this phenomenon could result in an increase in risk of asthma. This phenomenon of limited inflammatory response in iron deficiency, and restored inflammatory response with iron repletion is well described in the infectious disease literature [39–42], so it is plausible that this same phenomenon could mediate the relationships between iron and asthma that were observed among those whose ferritin levels were below 20–30 ng/ml.

Ferritin is known to be an imperfect indicator of iron status, and without more invasive testing it is difficult to determine true body iron stores. However, this limitation was addressed by examining relationships with ferritin in the range of ferritin values that are strongly and linearly correlated with iron stores [9–12], as well as the full range of ferritin. We also examined sTfR, which reflects *tissue iron need*, and the sTfR-F Index, which is a robust measure of *total body iron* [43], and associations between these additional measures of iron status and asthma were consistent with those observed for ferritin. Since ferritin was most consistently and strongly associated with the asthma outcomes, it is likely that iron stores, rather than tissue iron or body iron, plays a more important role in determining asthma risk. It is also possible that the lack of significant relationships between sTfR and the asthma outcomes could be due to the fact that sTfR is most strongly related to iron status in the setting of low ferritin levels [13,43], so it may not accurately capture iron status for most of the study population, resulting in weak and non-significant relationships with asthma.

While our findings are novel and suggest that iron status deserves further study as a potential cause of asthma, there are several additional limitations that should be considered. As our sample includes women only, it is unknown whether these findings are applicable to men. It is also possible that our findings with respect to ferritin were confounded by inflammation since ferritin is an acute-phase reactant and is known to be elevated in inflammatory states. However, higher ferritin was associated with a lower risk of asthma, rather than a higher risk of asthma as would be expected if ferritin were simply serving as a marker of an inflammatory disease. Furthermore, sensitivity analyses removing subjects with evidence of systemic inflammation did not alter our results. Iron status may act as an indicator of nutritional status or aspects of diet not investigated or controlled for in these analyses, though the supplementation studies discussed above are suggestive of an independent effect. Lastly, in a cross-sectional study, reverse causality cannot be excluded, so it is possible that having asthma leads to lower iron stores, which should be evaluated in prospective studies.

In summary, we found that higher iron stores were inversely associated with asthma and higher *tissue iron need* and lower *total body iron* were associated with lower lung function in US women. These findings, which are biologically plausible, merit further investigation in longitudinal studies and in other study populations, which will inform the need for randomized

controlled trials of iron supplementation for asthma prevention. Investigation of the role of iron status in asthma morbidity is also merited, given the findings in this study and the effect of iron on mast cells and eosinophils, which are known to play key roles in the asthmatic response. Should iron insufficiency prove to increase the risk of asthma, it would afford an opportunity to reduce the risk of asthma using an inexpensive intervention in a substantial number of individuals.

Supporting Information

S1 Table. Relationships between ferritin quintiles and asthma outcomes. *Adjusted for race/ethnicity, age, smoking, income, and BMI. n = 2906 for unadjusted, n = 2663 for adjusted. (DOCX)

S2 Table. Logistic and quadratic models of relationships between the full range of ferritin and asthma outcomes. All models adjusted for race/ethnicity, age, smoking, income, and BMI. **Bolded** results are statistically significant, with $p < 0.05$. *n = 2663. (DOCX)

S3 Table. Relationships between iron status and actual PFT values. Adjusted for race/ethnicity, age, smoking, income, height, and BMI. **Bolded** results are statistically significant, with $p < 0.05$. [‡] FEV₁ (n = 2236); FVC (n = 2201); FEF 25–75 (n = 2261). [§]Ferritin restricted to values from 20 to 300 ng/ml, inclusive; FEV₁ (n = 1657); FVC (n = 1633); FEF25–75 (n = 1676). [†] FEV₁ (n = 2233); FVC (n = 2198); FEF25–75 (n = 2258). [§]Q1–4: 1.8–76.0ng/ml, Q5: >76.0ng/ml. (DOCX)

S4 Table. Linear and quadratic models of relationships between the full range of ferritin and lung function and FeNO. All models adjusted for race/ethnicity, age, income, BMI, and smoking. **Bolded** results are statistically significant, with $p < 0.05$. *n = 2198; ^n = 2236; ^ϕn = 2201; [†] n = 2279. (DOCX)

S5 Table. Relationships between iron status and lung function and FeNO. Adjusted for race/ethnicity, age, smoking, income, and BMI. **Bolded** results are statistically significant, with $p < 0.05$. FEV₁/FVC (n = 2198); FEV₁ (n = 2236); FVC (n = 2201); FEF 25–75 (n = 2261); Log₁₀(FeNO) (n = 2279). (DOCX)

S6 Table. Relationships between iron deficiency, anemia, and asthma outcomes. *Adjusted for race/ethnicity, age, smoking, income, and BMI. Anemia was defined as a hemoglobin < 12.0 mg/dL and iron deficiency was defined as ferritin < 20 ng/mL. n = 2900 for unadjusted, n = 2658 for adjusted. (DOCX)

S7 Table. Relationships between iron deficiency, anemia, lung function and inflammation. Adjusted for race/ethnicity, age, smoking, income, and BMI. Anemia was defined as a hemoglobin < 12.0 mg/dL and iron deficiency was defined as ferritin < 20 ng/mL. [§]n = 2193; [†]n = 2274. (DOCX)

S8 Table. Relationships between iron status and asthma outcomes. *Adjusted for race/ethnicity, age, smoking, income, and BMI. **Bolded** results are statistically significant, with $p < 0.05$. [‡]n = 1046 for unadjusted, n = 930 for adjusted; Q1–4: 1.8–48.0ng/ml, Q5: >48.0ng/ml.

[§]ferritin restricted to values from 20 to 300 ng/ml, inclusive; n = 693 for unadjusted, n = 621 for adjusted. [†]n = 1043 for unadjusted, n = 927 for adjusted. (DOCX)

Author Contributions

Conceived and designed the experiments: ECM CMT MCM EPB. Performed the experiments: EPB ECM MCM. Analyzed the data: EPB ECM. Wrote the paper: EPB MCM CMT ECM.

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Table S1. Relationships between ferritin quintiles and asthma outcomes.

	Lifetime Asthma		Current Asthma		Asthma Attack/Episode in Past Year	
	Unadjusted	Adjusted*	Unadjusted	Adjusted*	Unadjusted	Adjusted*
Ferritin	OR (95% CI)		OR (95% CI)		OR (95% CI)	
Quintile 1 (1.8-15.7 ng/ml)	-ref-	-ref-	-ref-	-ref-	-ref-	-ref-
Quintile 2 (16-28.7 ng/ml)	1.11 (0.78 to 1.57)	1.08 (0.74 to 1.56)	1.14 (0.68 to 1.88)	1.25 (0.70 to 2.21)	1.46 (0.78 to 2.75)	1.78 (0.88 to 3.59)
Quintile 3 (29-46.6 ng/ml)	0.95 (0.65 to 1.38)	0.90 (0.62 to 1.31)	0.97 (0.58 to 1.61)	1.01 (0.59 to 1.72)	1.22 (0.67 to 2.25)	1.43 (0.75 to 2.73)
Quintile 4 (47-76 ng/ml)	1.17 (0.83 to 1.66)	1.12 (0.78 to 1.62)	1.16 (0.74 to 1.81)	1.20 (0.75 to 1.93)	1.40 (0.82 to 2.36)	1.52 (0.87 to 2.66)
Quintile 5 (76.8-1051.2 ng/ml)	0.81 (0.54 to 1.21)	0.71 (0.48 to 1.04)	0.89 (0.53 to 1.50)	0.72 (0.42 to 1.23)	1.09 (0.63 to 1.91)	0.81 (0.51 to 1.30)

*Adjusted for race/ethnicity, age, smoking, income, and BMI
n=2906 for unadjusted, n=2663 for adjusted

Table S2. Logistic and quadratic models of relationships between the full range of ferritin and asthma outcomes.

	Lifetime Asthma*		Current Asthma*		Asthma Attack/Episode in Past Yr*	
	Linear Model	Quadratic Model	Linear Model	Quadratic Model	Linear Model	Quadratic Model
	OR (95% CI)		OR (95% CI)		OR (95% CI)	
Log ₁₀ (ferritin)	0.81 (0.64 to 1.04)	3.41 (1.09 to 10.68)	0.77 (0.57 to 1.04)	8.65 (1.10 to 68.10)	0.84 (0.65 to 1.09)	12.32 (0.46 to 327.19)
[Log ₁₀ (ferritin)] ²	--	0.61 (0.42 to 0.90)	--	0.44 (0.22 to 0.86)	--	0.41 (0.14 to 1.22)

All models adjusted for race/ethnicity, age, smoking, income, and BMI

Bolded results are statistically significant, with p<0.05

*n=2663

Table S3. Relationships between iron status and actual PFT values.

	FEV₁ (ml)	FVC (ml)	FEF 25-75 (ml/s)
	β (95% CI)	β (95% CI)	β (95% CI)
Ferritin Iron Indices (higher levels indicative of <i>more</i> iron)			
Log ₁₀ (ferritin) [‡]	8.2 (-31.0 to 47.4)	-29.2 (-76.4 to 18.0)	90.3 (8.4 to 172.2)
Log ₁₀ (ferritin) [§] (20-300 ng/ml)	-55.9 (-145.0 to 33.2)	-132.7 (-249.9 to -15.5)	128.6 (-26.8 to 283.9)
Ferritin, quintile 5 vs. quintiles 1-4 [‡]	0.3 (-43.1 to 43.6)	-44.3 (-106.7 to 18.1)	91.9 (-7.8 to 191.5)
Serum Transferrin Receptor Iron Indices (higher levels indicative of <i>less</i> iron)			
Log ₁₀ (sTfR) [†]	-136.2 (-251.8 to -20.6)	-104.7 (-274.2 to 64.8)	-274.5 (-465.7 to -83.4)
Log ₁₀ (sTfR/log ₁₀ ferritin) [†]	-66.4 (-132.0 to -0.9)	-31.0 (-123.6 to 61.7)	-169.4 (-284.3 to -54.6)

Adjusted for race/ethnicity, age, smoking, income, height, and BMI

Bolded results are statistically significant, with p<0.05

[‡] FEV₁ (n=2236); FVC (n= 2201); FEF 25-75 (n=2261)

[§]Ferritin restricted to values from 20 to 300 ng/ml, inclusive; FEV₁ (n=1657); FVC (n=1633); FEF25-75 (n=1676)

[†] FEV₁ (n=2233); FVC (n=2198); FEF25-75 (n=2258)

[§]Q1-4: 1.8-76.0ng/ml, Q5: >76.0ng/ml

Table S4. Linear and quadratic models of relationships between the full range of ferritin and lung function and FeNO.

	FEV₁/FVC ratio*		FEV₁ % predicted[^]		FVC % predicted[†]		Log₁₀(FeNO)[‡]	
	Linear Model	Quadratic Model	Linear Model	Quadratic Model	Linear Model	Quadratic Model	Linear Model	Quadratic Model
	β (95% CI)		β (95% CI)		β (95% CI)		β (95% CI)	
Log ₁₀ (ferritin)	0.009 (0.003 to 0.01)	-0.007 (-0.05 to 0.04)	0.18 (-0.99 to 1.35)	8.53 (-0.25 to 17.31)	-0.77 (-1.98 to 0.44)	9.08 (0.80 to 17.37)	-0.01 (-0.05 to 0.03)	0.11 (-0.07 to 0.28)
[Log ₁₀ (ferritin)] ²	--	0.005 (-0.009 to 0.02)	--	-2.81 (-5.78 to 0.15)	--	-3.32 (-6.09 to -0.55)	--	-0.04 (-0.10 to 0.02)

All models adjusted for race/ethnicity, age, income, BMI, and smoking

Bolded results are statistically significant, with p<0.05

*n=2198; ^n=2236; †n=2201; ‡n=2279

Table S5. Relationships between iron status and lung function and FeNO.

	FEV₁/FVC ratio	FEV₁ % predicted	FVC % predicted	FEF 25-75 % predicted	Log₁₀(FeNO)
Ferritin	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)
Quintile 1 (1.8-15.7 ng/ml)	-ref-	-ref-	-ref-	-ref-	-ref-
Quintile 2 (16-28.7 ng/ml)	0.003 (-0.004 to 0.01)	0.48 (-1.46 to 2.41)	-0.05 (-2.05 to 1.96)	0.15 (-2.93 to 3.23)	0.03 (-0.02 to 0.07)
Quintile 3 (29-46.6 ng/ml)	-0.00002 (-0.01 to 0.01)	1.31 (-0.81 to 3.42)	1.42 (-0.86 to 3.70)	0.93 (-3.03 to 4.90)	0.03 (-0.02 to 0.07)
Quintile 4 (47-76 ng/ml)	0.005 (-0.003 to 0.01)	0.15 (-1.89 to 2.19)	-0.49 (-2.58 to 1.60)	1.46 (-1.92 to 4.83)	0.007 (-0.04 to 0.05)
Quintile 5 (76.8-1051.2 ng/ml)	0.01 (0.003 to 0.02)	0.39 (-1.23 to 2.02)	-0.87 (-2.66 to 0.92)	3.09 (-0.59 to 6.78)	-0.01 (-0.06 to 0.03)

Adjusted for race/ethnicity, age, smoking, income, and BMI

Bolded results are statistically significant, with p<0.05

FEV₁/FVC (n=2198); FEV₁ (n=2236); FVC (n=2201); FEF 25-75 (n=2261); Log₁₀(FeNO) (n=2279)

Table S6. Relationships between iron deficiency, anemia, and asthma outcomes.

		Lifetime Asthma		Current Asthma		Asthma Attack/Episode in Past Year	
		Unadjusted	Adjusted*	Unadjusted	Adjusted*	Unadjusted	Adjusted*
	Iron status	OR (95% CI)		OR (95% CI)		OR (95% CI)	
No anemia	Sufficient	-ref-	-ref-	-ref-	-ref-	-ref-	-ref-
	Deficient	0.91 (0.65 to 1.26)	0.97 (0.69 to 1.37)	0.94 (0.60 to 1.46)	0.96 (0.61 to 1.53)	0.85 (0.48 to 1.48)	0.84 (0.47 to 1.52)
Anemia	Sufficient	0.91 (0.51 to 1.63)	0.94 (0.53 to 1.67)	0.95 (0.38 to 2.34)	0.79 (0.32 to 1.93)	0.95 (0.34 to 2.68)	0.95 (0.30 to 3.05)
	Deficient	0.84 (0.55 to 1.28)	0.95 (0.64 to 1.40)	0.82 (0.53 to 1.28)	0.90 (0.56 to 1.45)	0.85 (0.46 to 1.55)	0.99 (0.53 to 1.85)

*Adjusted for race/ethnicity, age, smoking, income, and BMI

Anemia was defined as a hemoglobin < 12.0 mg/dL and iron deficiency was defined as ferritin <20 ng/mL

n=2900 for unadjusted, n=2658 for adjusted

Table S7. Relationships between iron deficiency, anemia, lung function and inflammation.

		FEV₁/FVC ratio[§]	Log₁₀(FeNO)[†]
	Iron-status	β (95% CI)	β (95% CI)
No anemia	Sufficient	-ref-	-ref-
	Deficient	-0.006 (-0.01 to 0.001)	-0.02 (-0.06 to 0.02)
Anemia	Sufficient	-0.007 (-0.03 to 0.01)	-0.06 (-0.1 to 0.03)
	Deficient	-0.0007 (-0.01 to 0.01)	-0.007 (-0.07 to 0.05)

Adjusted for race/ethnicity, age, smoking, income, and BMI

Anemia was defined as a hemoglobin <12.0 mg/dL and iron deficiency was defined as ferritin <20 ng/mL

[§]n=2193; [†]n=2274

Table S8. (age 12 to 19) Relationships between iron status and asthma outcomes.

	Lifetime Asthma		Current Asthma		Asthma Attack/Episode in Past Year	
	Unadjusted	Adjusted*	Unadjusted	Adjusted*	Unadjusted	Adjusted*
	OR (95% CI)		OR (95% CI)		OR (95% CI)	
Ferritin Iron Indices (higher levels indicative of <i>more</i> iron)						
Log ₁₀ (ferritin) [‡]	0.96 (0.56 to 1.64)	0.96 (0.55 to 1.65)	1.16 (0.56 to 2.39)	1.20 (0.54 to 2.69)	0.59 (0.24 to 1.49)	0.55 (0.23 to 1.33)
Log ₁₀ (ferritin) [§] _(20-300 ng/ml)	1.48 (0.43 to 5.08)	1.29 (0.33 to 5.09)	4.33 (0.98 to 19.24)	4.15 (0.70 to 24.62)	1.59 (0.17 to 15.09)	0.75 (0.08 to 7.13)
Ferritin, quintile 5 vs. quintiles 1-4 [‡]	1.20 (0.76 to 1.90)	1.12 (0.67 to 1.87)	1.54 (0.87 to 2.71)	1.45 (0.71 to 2.97)	1.17 (0.50 to 2.71)	0.89 (0.36 to 2.20)
Serum Transferrin Receptor Iron Indices (higher levels indicative of <i>less</i> iron)						
Log ₁₀ (sTfR) [†]	1.50 (0.55 to 4.06)	1.34 (0.41 to 4.42)	1.66 (0.50 to 5.51)	1.41 (0.29 to 6.83)	4.45 (1.04 to 19.13)	6.13 (1.16 to 32.43)
Log ₁₀ (sTfR/log ₁₀ ferritin) [†]	1.21 (0.60 to 2.42)	1.14 (0.53 to 2.45)	1.14 (0.46 to 2.83)	1.02 (0.33 to 3.09)	2.61 (0.97 to 7.00)	2.97 (1.01 to 8.71)

*Adjusted for race/ethnicity, age, smoking, income, and BMI

Bolded results are statistically significant, with p<0.05

[‡]n=1046 for unadjusted, n=930 for adjusted; Q1-4: 1.8-48.0ng/ml, Q5: >48.0ng/ml

[§]ferritin restricted to values from 20 to 300 ng/ml, inclusive; n=693 for unadjusted, n=621 for adjusted

[†]n=1043 for unadjusted, n=927 for adjusted

S1_Fig.png

<div><p>(A) Heatmap showing the 81 clinical biomarkers (X axis) for all subjects (Y axis). (B) Heatmap showing the gene expression (X axis) for 901 genes used in downstream analyses for all 192 subjects (Y axis). For both panels, values are scaled by column using Z scores. Asthma status based on doctor diagnosis is indicated on the left hand side of the heatmap (red = no asthma, green = asthma, blue = unknown). The total number of asthmatics is 96 and the total number of non-asthmatics is 88. Eight individuals did not have a reported asthma status from the doctor diagnosis.</p>

</div>

10.1371/journal.pone.0117445.s001

S2_Fig.jpeg

<div><p>The networks were generated through the use of Ingenuity Pathways Analysis (Ingenuity Systems, www.ingenuity.com). The loading value for each gene was imported in place of an expression value, so green nodes (negative loadings) indicate a gene associated with the left branch (Down) of the metagene whereas red nodes (positive loadings) indicate genes associated with the right branch (Up).</p>

</div>

10.1371/journal.pone.0117445.s002

S3_Fig.jpeg

<div><p>The networks were generated through the use of Ingenuity Pathways Analysis (Ingenuity Systems, www.ingenuity.com). The loading value for each gene was imported in place of an expression value, so green nodes (negative loadings) indicate a gene associated with the left branch (Down) of the metagene whereas red nodes (positive loadings) indicate genes associated with the right branch (Up).</p>

</div>

10.1371/journal.pone.0117445.s003

S4_Fig.jpeg

<div><p>The networks were generated through the use of Ingenuity Pathways Analysis (Ingenuity Systems, www.ingenuity.com). The loading value for each gene was imported in place of an expression value, so green nodes (negative loadings) indicate a gene associated with the left branch (Down) of the metagene whereas red nodes (positive loadings) indicate genes associated with the right branch (Up).</p>

</div>

10.1371/journal.pone.0117445.s004

S5_Fig.jpeg

<div><p>The networks were generated through the use of Ingenuity Pathways Analysis (Ingenuity Systems, www.ingenuity.com). The loading value for each gene was imported in place of an expression value, so green nodes (negative loadings) indicate a gene associated with the left branch (Down) of the metagene whereas red nodes (positive loadings) indicate genes associated with the right branch (Up). See S6 Fig. for the second highest scoring IPA network for E:PC2 since its score was still reasonably high relative to the top scoring network (S3 Table).</p>

</div>

10.1371/journal.pone.0117445.s005

S6_Fig.jpeg

<div><p>The networks were generated through the use of Ingenuity Pathways Analysis (Ingenuity Systems, www.ingenuity.com). The loading value for each gene was imported in place of an expression value, so green nodes (negative loadings)

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indicate a gene associated with the left branch (Down) of the metagene whereas red nodes (positive loadings) indicate genes associated with the right branch (Up). Second highest scoring IPA network for E:PC2 since its score was still reasonably high relative to the top scoring network (<http://www.plosone.org/article/info:doi/10.1371/journal.pone.0117445#pone.0117445.s012>) (S3 Table).

</div>

10.1371/journal.pone.0117445.s006

s7_Fig.jpeg

The networks were generated through the use of Ingenuity Pathways Analysis (Ingenuity Systems, <http://www.ingenuity.com> target="_blank">www.ingenuity.com). The loading value for each gene was imported in place of an expression value, so green nodes (negative loadings) indicate a gene associated with the left branch (Down) of the metagene whereas red nodes (positive loadings) indicate genes associated with the right branch (Up).

10.1371/journal.pone.0117445.s007

S8_Fig.jpeg

The networks were generated through the use of Ingenuity Pathways Analysis (Ingenuity Systems, <http://www.ingenuity.com> target="_blank">www.ingenuity.com). The loading value for each gene was imported in place of an expression value, so green nodes (negative loadings) indicate a gene associated with the left branch (Down) of the metagene whereas red nodes (positive loadings) indicate genes associated with the right branch (Up). See

10.1371/journal.pone.0117445.s008

S9_Fig.jpeg

The networks were generated through the use of Ingenuity Pathways Analysis (Ingenuity Systems, <http://www.ingenuity.com>). The loading value for each gene was imported in place of an expression value, so green nodes (negative loadings) indicate a gene associated with the left branch (Down) of the metagene whereas red nodes (positive loadings) indicate genes associated with the right branch (Up). Second highest scoring IPA network for J:PC2 since its score was still reasonably high relative to the top scoring network (<http://www.plosone.org/article/info:doi/10.1371/journal.pone.0117445#pone.0117445.s012>) S3 Table).

10.1371/journal.pone.0117445.s009

S1_Table.docx

Results from a forward-reverse multi-step regression of each metagene from the asthma decision tree on the white blood cell counts and percentage of each individual cell type. Overall contribution of relative changes in cell type was based on the Adjusted R^2 coefficient of determination. The sign of the parameter estimate was used to determine the branch of the tree associated with the cell type.

</div>

10.1371/journal.pone.0117445.s010

s2 Table.docx

<div><p>B-PC1 and F-PC2 had only one significant network each. For all other metagenes, the highest scoring network that was not considered is included and the score shown. Full page views of all networks considered in the interpretation phase are shown in S2-<a

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href="http://www.plosone.org/article/info:doi/10.1371/journal.pone.0117445#pone.0117445.s009" target="_blank">S9 Figs.</p>
</div>
10.1371/journal.pone.0117445.s011

S3_Table.docx

<div><p>Geometric means and CIs were calculated using SAS-callable SUDAAN [57]; other statistics were calculated using SAS [58].</p>
</div>
10.1371/journal.pone.0117445.s012

S4_Table.docx

10.1371/journal.pone.0117445.s013

S5_Table.xlsx

<div><p>Gene symbols as of the date of analysis along with Affymetrix probe ids are provided. Clusters are identified by color (from the dendrogram) and letter (from labels) in reference to Fig. 1A of the main manuscript.</p>
</div>
10.1371/journal.pone.0117445.s014

S6_Table.docx

10.1371/journal.pone.0117445.s015

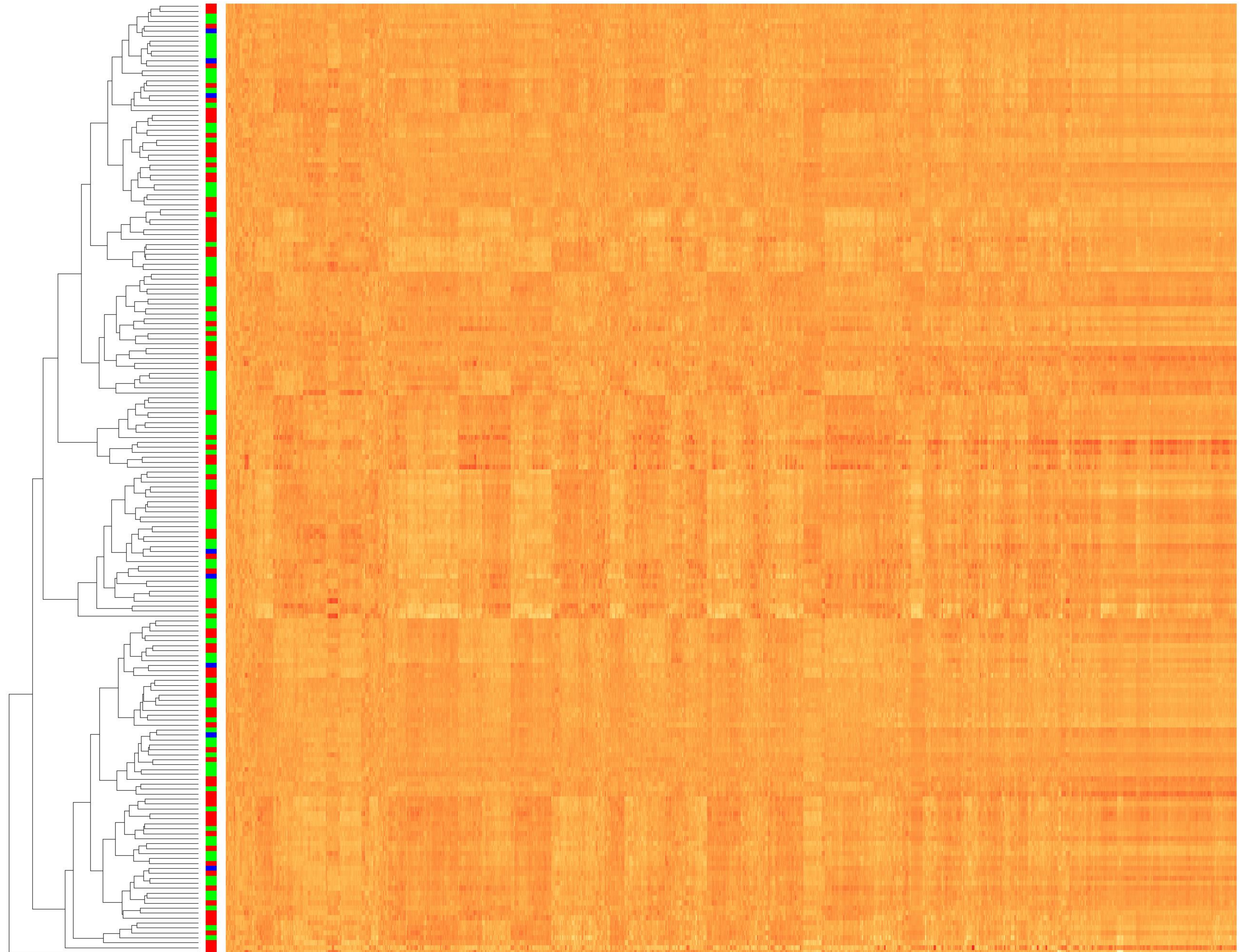
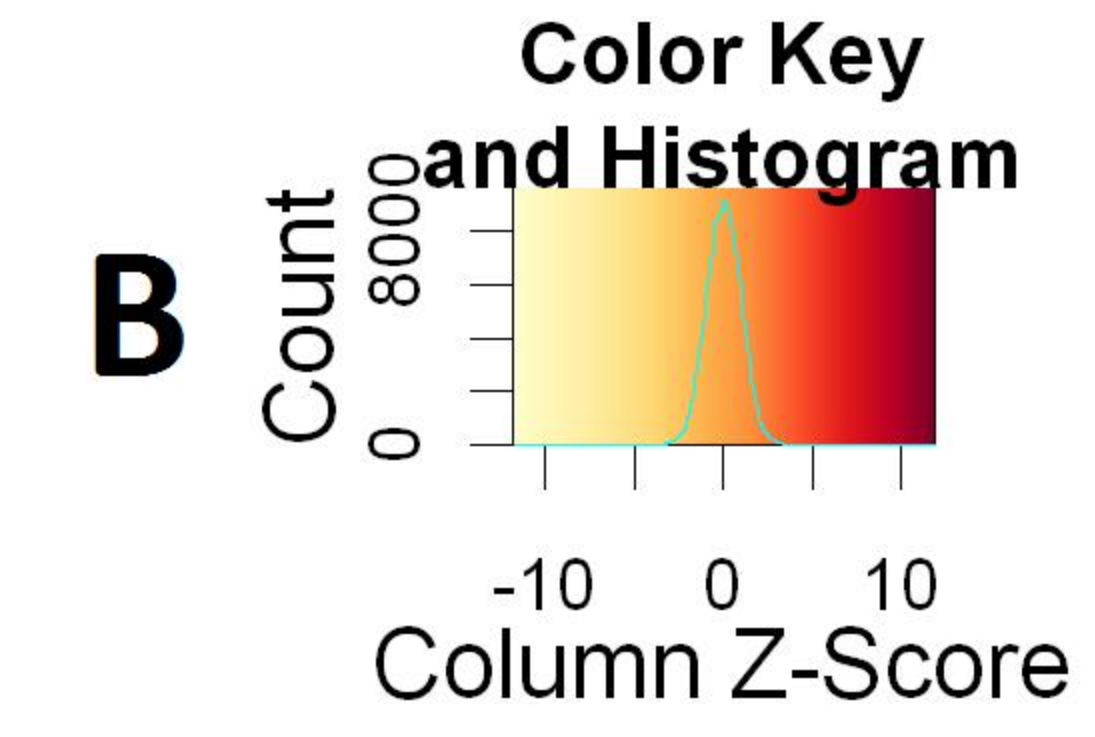
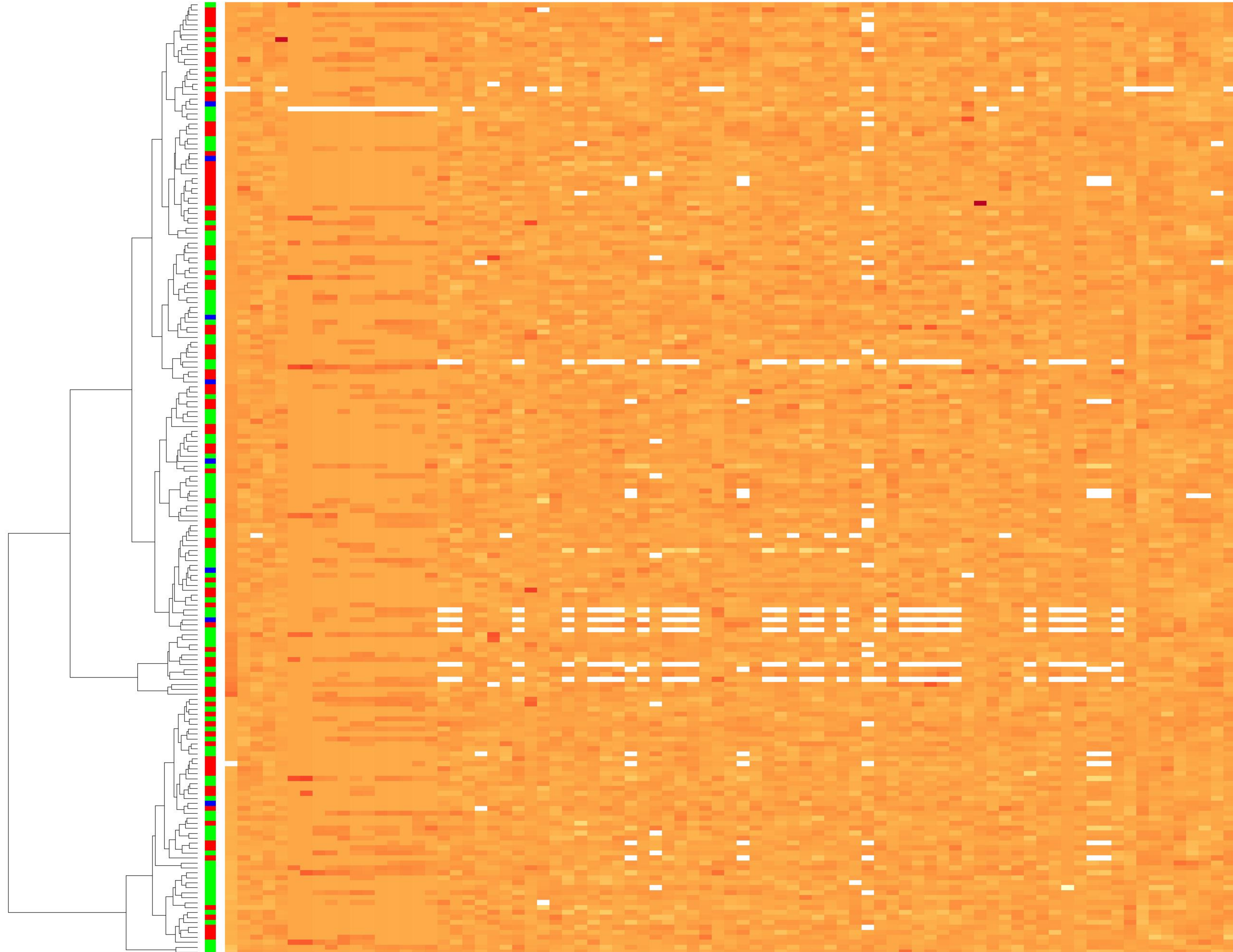
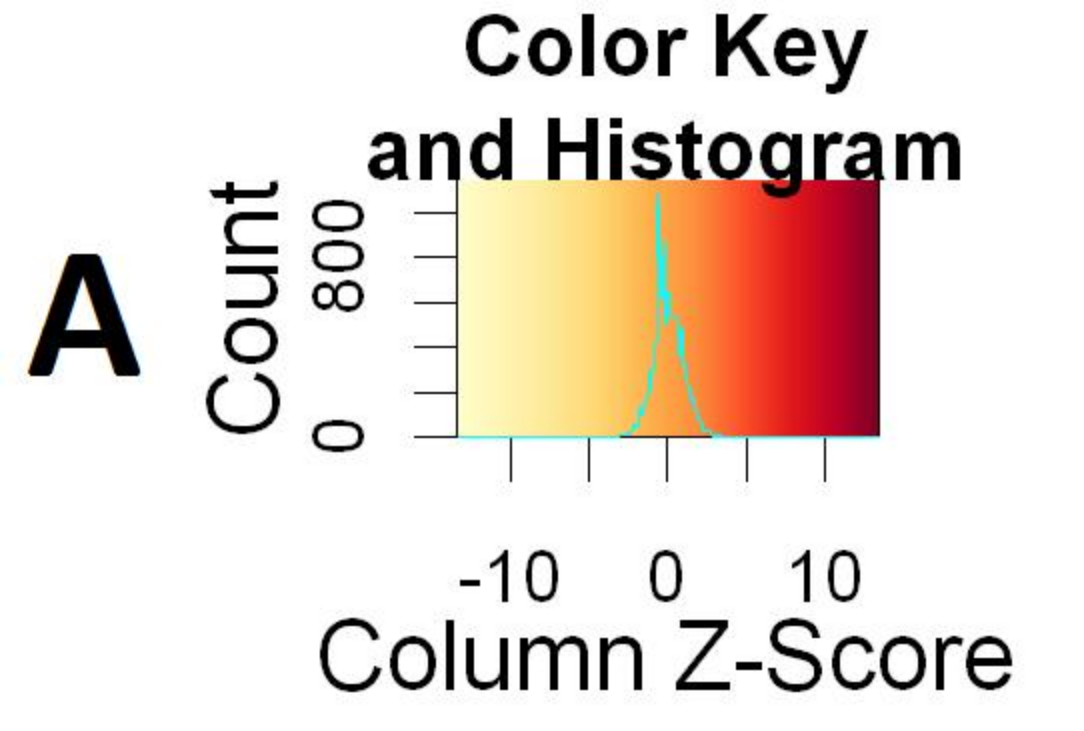


Table S1. Contribution of cell type to metagene summarized expression. Results from a forward-reverse multi-step regression of each metagene from the asthma decision tree on the white blood cell counts and percentage of each individual cell type. Overall contribution of relative changes in cell type was based on the Adjusted R^2 coefficient of determination. The sign of the parameter estimate was used to determine the branch of the tree associated with the cell type.

Metagene*	Covariate	Parameter Estimate	p-value	Adjusted R ²	Condition Index [‡]
K-PC1 (Leaves 1-8)	Intercept	-0.06	0.8288	0.6167	1.00
	Percent Blood Lymphocytes	0.04	<.0001		3.27
	Percent Blood Eosinophils	-0.43	<.0001		9.67
B-PC2 (Leaves 1-3)	Intercept	3.18	<.0001	0.3656	1.00
	Percent Blood Lymphocytes	-0.12	<.0001		6.65
	Percent Blood Monocytes	0.19	0.0001		10.64
B-PC1 (Leaves 4-8)	Intercept	3.24	<.0001	0.3508	1.00
	Percent Blood Lymphocytes	0.04	0.0066		6.65
	Percent Blood Monocytes	-0.67	<.0001		10.64
C-PC2 (Leaves 2-3)	(no model)^				
J-PC2 (Leaves 4-6)	(no model)^				
F-PC2 (Leaves 7-8)	Intercept	-8.34	0.0029	0.0484	1.00
	Percent Blood Lymphocytes	0.11	0.0014		5.33
	Percent Blood Neutrophils	0.08	0.0068		55.62
E-PC2 (Leaves 4-5)	Intercept	-4.27	0.0003	0.0638	1.00
	Percent Blood Neutrophils	0.09	0.0002		9.07

* Notation for metagenes is Cluster Letter followed by Principal Component (i.e. Cluster K, Principal Component 1 = K-PC1)

† Collinearity diagnostic where 10 may indicate weak dependencies and increasing severity with higher indexes

^ No variable met the 0.2000 significance level for entry into the model.

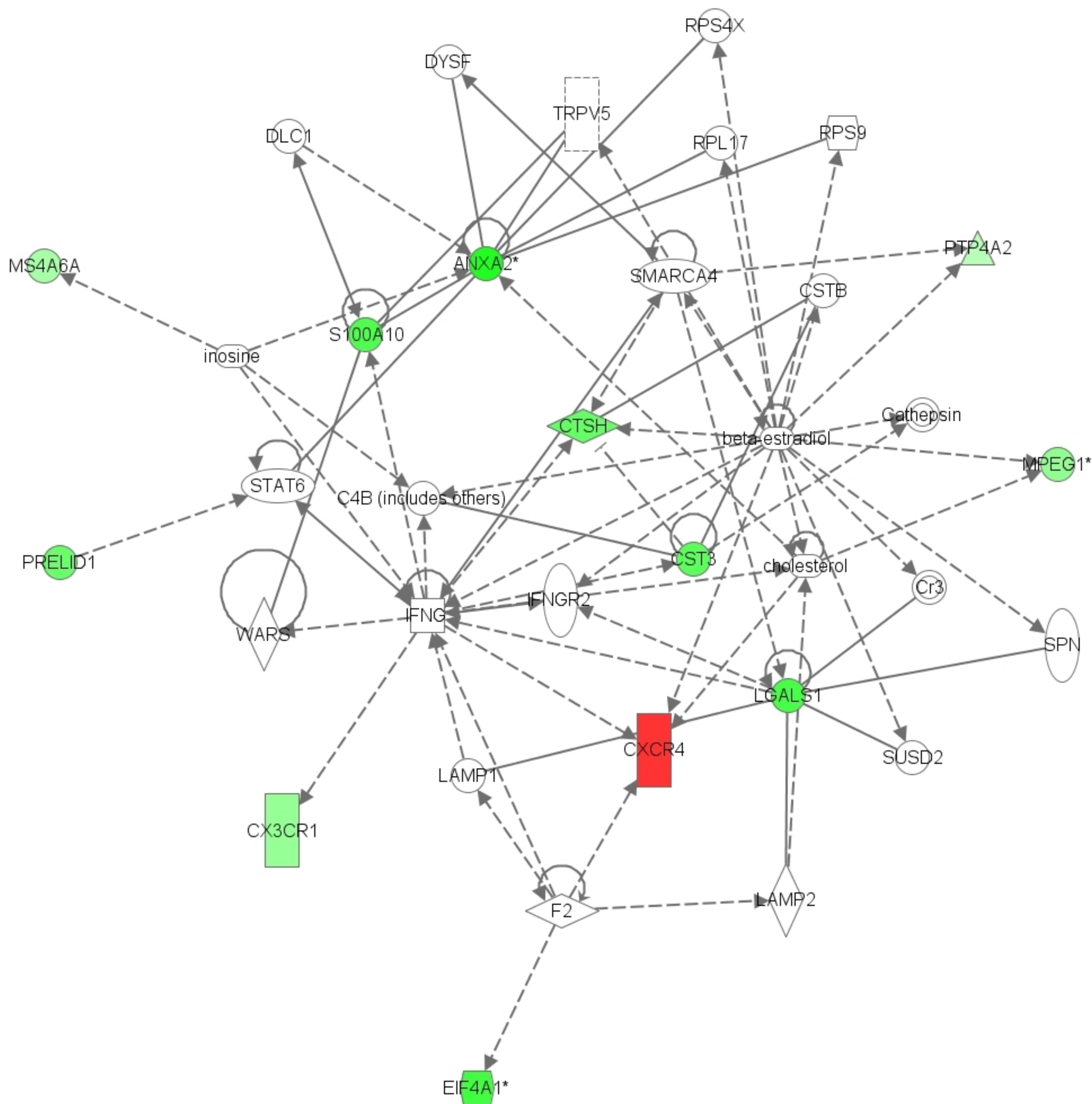


Table S2. Top scoring Ingenuity Pathways Analysis networks with associated annotations. B-PC1 and F-PC2 had only one significant network each. For all other metagenes, the highest scoring network that was not considered is included and the score shown. Full page views of all networks considered in the interpretation phase are shown in Figures S2-S9.

Metagene	Network			Associated Network Functions
	Rank	Score	Figure	
B-PC1	1	35	S2	Cellular Movement, Hematological System Development and Function, Immune Cell Trafficking
B-PC2	1	27	S3	Cell-to-Cell Signaling and Interaction, Cell Death, Cellular Growth and Proliferation
	2	6		Not considered
C-PC2	1	66	S4	Protein Synthesis, Cell Death, Gene Expression
	2	24		Not considered
E-PC2	1	33	S5	Protein Synthesis, RNA Post-Transcriptional Modification, DNA Replication, Recombination, and Repair
	2	24	S6	Gene Expression, Cellular Development, Cellular Growth and Proliferation
	3	3		Not considered
F-PC2	1	33	S7	Cardiac Necrosis/Cell Death, Cell Death, Gene Expression
J-PC2	1	24	S8	Free Radical Scavenging, Cell-to-Cell Signaling and Interaction, Hematological System Development and Function
	2	21	S9	Cellular Assembly and Organization, Gene Expression, Cardiovascular Disease
	3	3		Not considered

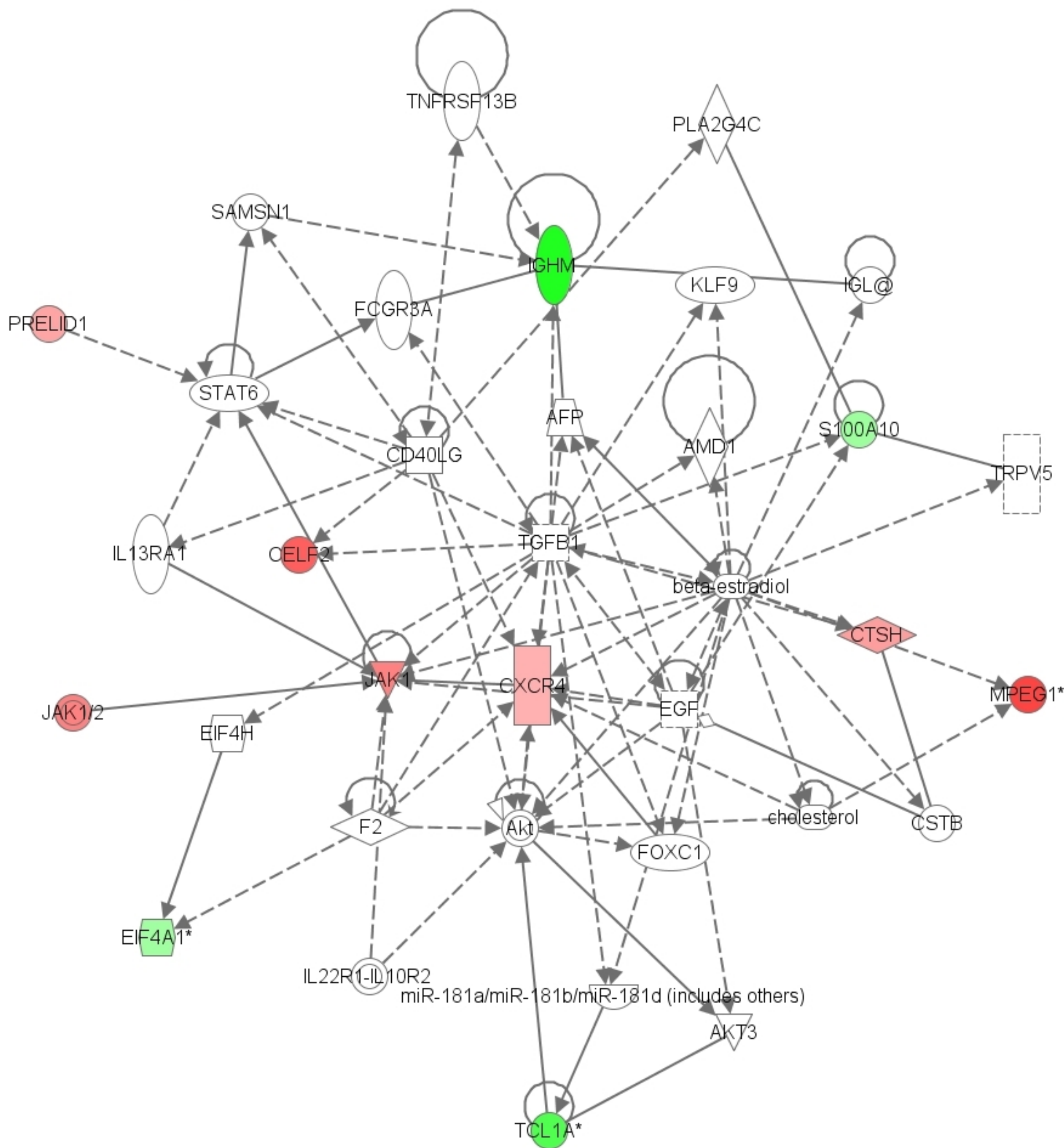


Table S3. Inflammation/allergy-related characteristics of subjects by leaf (*potential asthma endotype)

Leaf	1*	2*	3	4	5*	6	7	8*
Sample Size (n)	30	14	15	14	15	29	14	15
Asthma	90.0	71.4	26.7	21.4	60.0	6.9	42.9	73.3
Median Age (Yrs)	12.0	11.2	12.0	11.6	11.7	11.3	11.9	11.3
Male	63.3	71.4	66.7	71.4	46.7	41.4	71.4	46.7
African-American	83.3	71.4	53.3	64.3	80.0	86.2	85.7	80.0
Atopic	96.6	71.4	100.0	35.7	53.3	41.4	71.4	33.3
Eosinophilic	43.3	28.6	53.3	7.1	0.0	0.0	0.0	0.0
Geometric Mean (95% CI)								
Total Serum IgE (kU/L)	348.9 (204.6, 493.2)	117.7 (43.4, 192.0)	218.8 (117.7, 319.9)	42.0 (5.3, 78.8)	67.4 (15.3, 119.6)	49.0 (20.2, 77.8)	131.2 (17.5, 244.9)	36.1 (3.4, 68.8)
Phadiatop (kUA/L)	23.9 (10.6, 37.2)	3.5 (0.0, 7.9)	17.1 (5.0, 29.3)	1.1 (0.0, 2.6)	1.6 (0.0, 3.5)	0.9 (0.2, 1.7)	2.7 (0.0, 5.7)	0.9 (0.0, 1.9)
Food Screen Fx5e (kUA/L)	1.6 (0.5, 2.8)	0.3 (0.2, 0.5)	0.4 (0.2, 0.5)	0.3 (0.0, 0.6)	0.3 (0.0, 0.6)	0.4 (0.2, 0.5)	0.4 (0.1, 0.7)	0.2 (0.1, 0.3)
Blood Eosinophils (K/uL)	0.4 (0.3, 0.4)	0.3 (0.2, 0.4)	0.4 (0.3, 0.5)	0.2 (0.1, 0.2)	0.1 (0.1, 0.2)	0.1 (0.1, 0.2)	0.1 (0.1, 0.2)	0.1 (0.1, 0.1)
Blood Neutrophils (K/uL)	2.7 (2.2, 3.1)	3.3 (2.4, 4.3)	4.0 (3.2, 4.9)	2.4 (2.1, 2.6)	3.7 (3.0, 4.4)	3.0 (2.4, 3.6)	3.2 (2.2, 4.1)	3.4 (3.1, 3.8)
Blood Lymphocytes (K/uL)	2.7 (2.4, 2.9)	2.2 (2.0, 2.5)	2.7 (2.5, 3.0)	2.5 (2.4, 2.7)	2.4 (2.1, 2.8)	2.7 (2.4, 2.9)	2.5 (2.0, 2.9)	2.6 (2.3, 2.9)
Blood Monocytes (K/uL)	0.4 (0.4, 0.5)	0.5 (0.4, 0.6)	0.5 (0.4, 0.6)	0.4 (0.4, 0.5)	0.5 (0.4, 0.6)	0.5 (0.5, 0.6)	0.3 (0.3, 0.4)	0.4 (0.3, 0.4)
Total White Blood Cells (K/uL)	6.3 (5.7, 7.0)	6.8 (5.6, 7.9)	7.8 (6.7, 8.9)	5.5 (5.2, 5.9)	6.9 (5.9, 7.9)	6.5 (5.7, 7.3)	6.5 (5.5, 7.5)	6.6 (6.1, 7.1)
Exhaled nitric oxide (ppb)	27.2 (18.3, 36.1)	21.6 (11.6, 31.5)	21.7 (9.7, 33.7)	10.1 (6.9, 13.3)	13.3 (8.7, 17.9)	10.5 (6.8, 14.1)	14.1 (7.4, 20.7)	8.4 (5.3, 11.5)

Note: Selected demographics (top) are reported as percentages unless noted. The geometric means and 95% confidence intervals (CIs) for inflammation and allergy-related biomarkers (bottom) for each leaf in the decision tree (Figure 1B). Asthma status of the subjects was determined by doctor diagnosis; *indicates leaf where the majority of the subjects have asthma. Phadiatop is a single analysis that measures the relative level of IgE antibody specific for a panel of 10 common aeroallergens. Subjects were defined as atopic when phadiatop ≥ 0.35 kUA/L. Eosinophilia was defined as blood eosinophils > 0.4 K/uL. Total Serum IgE (kU/L) < 2.0 was changed to 1. Phadiatop (kUA/L) and Fx5e Food Screen (kUA/L) values < 0.35 were changed to 0.175 and > 100 were changed to 101. The 95% CIs were left truncated at 0. Geometric means and CIs were calculated using SAS-callable SUDAAN [57]; other statistics were calculated using SAS [58].

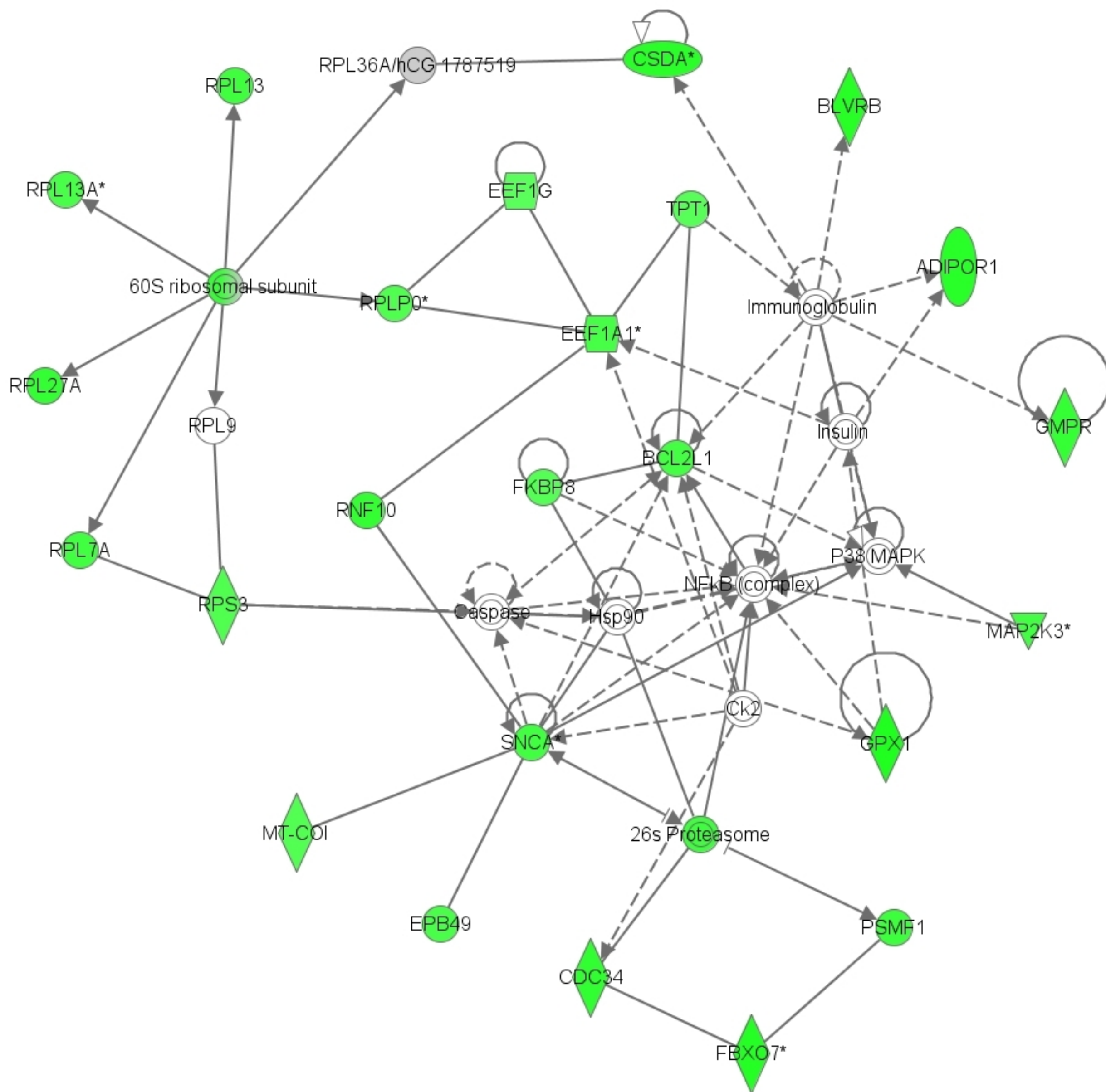
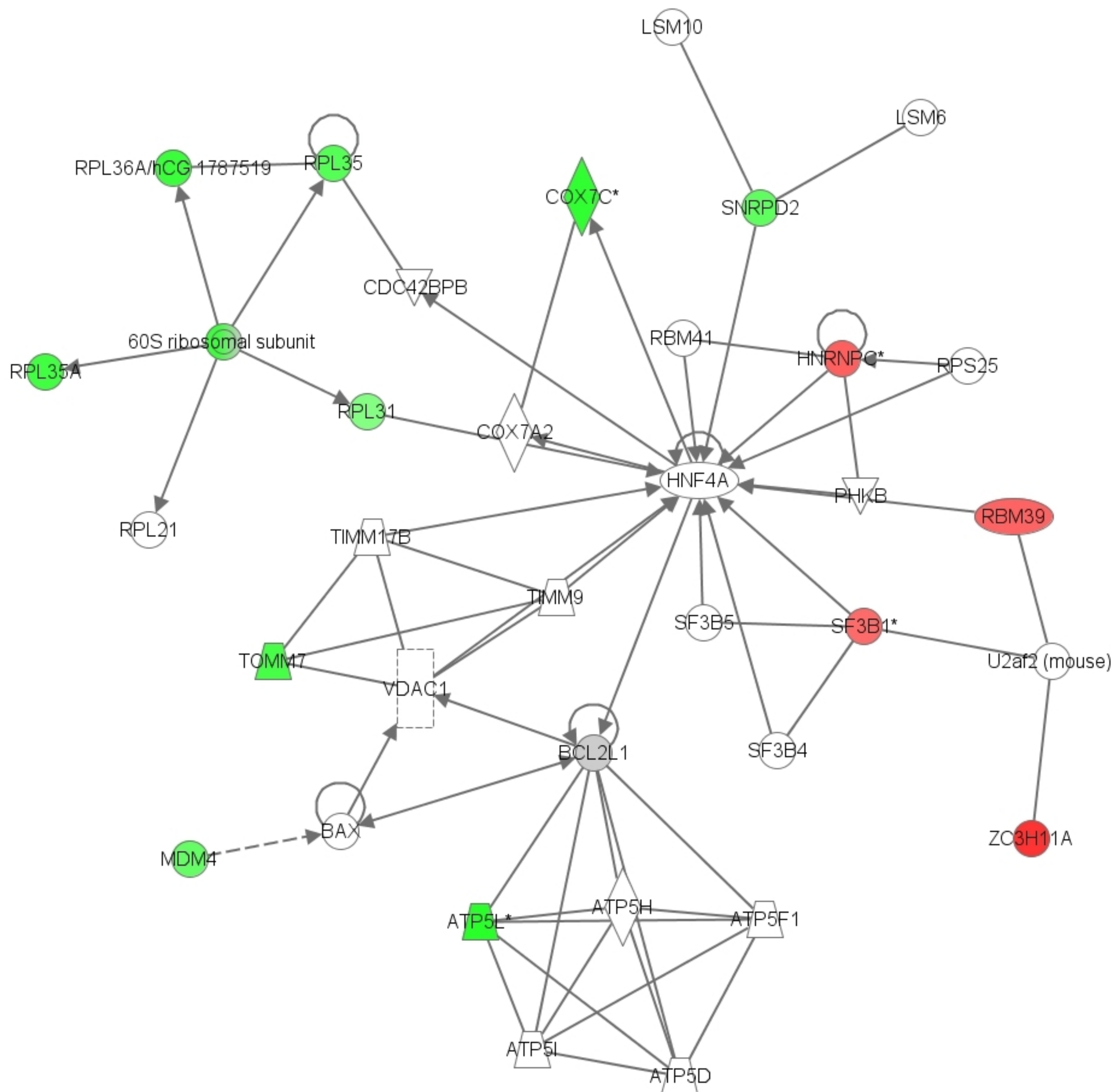


Table S4. Metabolic syndrome-related clinical markers along with lung function and medication use by leaf (*potential asthma endotype)

Leaf	1*	2*	3	4	5*	6	7	8*
Sample Size (n)	30	14	15	14	15	29	14	15
Asthma (n)	27	10	4	3	9	2	6	11
No asthma (n)	3	4	11	11	6	27	8	4
Geometric Mean (95% CI)								
BMI [weight(kg)/ height(m) ²]	21.8 (19.9, 23.7)	21.9 (18.5, 25.3)	21.4 (19.3, 23.6)	18.3 (16.3, 20.4)	21.3 (18.8, 23.7)	23.6 (21.4, 25.8)	19.4 (16.6, 22.1)	21.7 (19.3, 24.2)
Serum Triglycerides (mg/dL)	73.4 (62.3, 84.6)	82.4 (67.5, 97.3)	85.9 (66.9, 105.0)	62.9 (53.7, 72.2)	66.7 (56.8, 76.5)	79.3 (66.4, 92.2)	68.3 (57.1, 79.5)	76.3 (58.6, 94.0)
Serum VLDL (mg/dL)	14.7 (12.4, 16.9)	16.5 (13.6, 19.4)	17.2 (13.5, 21.0)	12.5 (10.7, 14.3)	13.2 (11.1, 15.3)	15.9 (13.3, 18.5)	13.5 (11.3, 15.8)	15.2 (11.7, 18.7)
Plasma Leptin (ng/ml)	1.7 (0.8, 2.6)	1.9 (0.8, 3.0)	2.0 (0.5, 3.5)	2.1 (0.8, 3.5)	1.8 (0.7, 2.9)	3.5 (2.2, 4.9)	1.4 (0.4, 2.4)	2.4 (0.4, 4.3)
FEV1.0 / FVC ratio	79.9 (76.3, 83.6)	79.7 (74.4, 84.9)	86.7 (84.5, 88.8)	84.3 (82.3, 86.2)	81.2 (75.7, 86.8)	86.3 (84.0, 88.7)	81.8 (78.6, 84.9)	85.2 (82.7, 87.7)
Asthma Medication Use (% asthmatics)								
None	3.7	20.0	0.0	0.0	11.1	0.0	0.0	18.2
Occasional	48.2	20.0	75.0	33.3	22.2	0.0	33.3	36.4
Daily	18.5	30.0	25.0	66.7	44.4	100.0	50.0	27.3
2 Meds Daily	29.6	30.0	0.0	0.0	22.2	0.0	16.7	18.2

Note: Geometric means and 95% confidence intervals (CIs) per leaf in the decision tree for selected metabolic syndrome-related biomarkers found correlated with informative metagenes along with lung function and medication use. The 95% CIs were left truncated at 0. Geometric means and CIs were calculated using SAS-callable SUDAAN [57]; other statistics were calculated using SAS [58]. Medication use was calculated as the percentage of the total asthmatics in the group falling into each category.



Gene Symbol	Affymetrix Probe	Cluster Color	Cluster Letter
CCL5	1405_i_at	Hunter	H
CAPNS1	200001_at	Peach	C
RPL35	200002_at	Purple	E
EIF4G2	200004_at	Purple	E
SRP14	200007_at	Purple	E
GDI2	200009_at	Purple	E
RPL11	200010_at	Purple	E
RPL24	200013_at	Lime	D
HNRNPA1	200016_x_at	Olive	G
RPS27A	200017_at	Hunter	H
EIF3F	200023_s_at	Olive	G
RPS5	200024_at	Peach	C
RPL34	200026_at	Purple	E
RPL9	200032_s_at	Purple	E
RPL6	200034_s_at	Purple	E
RPL10A	200036_s_at	Olive	G
CBX3	200037_s_at	Purple	E
RPL17	200038_s_at	Purple	E
RHOA	200059_s_at	Hunter	H
RPS24	200061_s_at	Purple	E
RPL30	200062_s_at	Peach	C
NPM1	200063_s_at	Olive	G
ARF1	200065_s_at	Hunter	H
RPL14	200074_s_at	Olive	G
GUK1	200075_s_at	Lime	D
ATP6V0B	200078_s_at	Brown	I
H3F3A	200080_s_at	Hunter	H
RPS7	200082_s_at	Purple	E
COX4I1	200086_s_at	Hunter	H
RPL12	200088_x_at	Hunter	H
RPS25	200091_s_at	Hunter	H
HINT1	200093_s_at	Purple	E
EEF2	200094_s_at	Hunter	H
RPS10	200095_x_at	Peach	C
ATP6V0E1	200096_s_at	Hunter	H
LOC439992	200099_s_at	Purple	E
HSP90B1	200599_s_at	Lime	D
PRKAR1A	200603_at	Olive	G
PRKAR1A	200605_s_at	Olive	G
LASP1	200618_at	Olive	G
TMEM59	200620_at	Pink	F
CAP1	200625_s_at	Olive	G
MATR3	200626_s_at	Lime	D
PTGES3	200627_at	Lime	D
GABARAP	200645_at	Hunter	H
GLUL	200648_s_at	Hunter	H
CALM1	200653_s_at	Peach	C

S100A11	200660_at	Hunter	H
UBE2D3	200668_s_at	Hunter	H
NPC2	200701_at	Olive	G
LITAF	200704_at	Brown	I
EEF1B2	200705_s_at	Purple	E
LITAF	200706_s_at	Olive	G
FKBP1A	200709_at	Hunter	H
RPL13A	200715_x_at	Purple	E
RPL13A	200716_x_at	Peach	C
RPL7	200717_x_at	Purple	E
SKP1	200718_s_at	Hunter	H
ACTR2	200728_at	Purple	E
GPX1	200736_s_at	Peach	C
PGK1	200738_s_at	Olive	G
FTH1	200748_s_at	Olive	G
ARL6IP5	200761_s_at	Purple	E
PTMA	200772_x_at	Hunter	H
PTMA	200773_x_at	Hunter	H
HNRNPK	200775_s_at	Peach	C
GNAS	200780_x_at	Purple	E
RPS15A	200781_s_at	Peach	C
ODC1	200790_at	Hunter	H
IQGAP1	200791_s_at	Pink	F
DAZAP2	200794_x_at	Olive	G
MCL1	200797_s_at	Lightblue	J
MCL1	200798_x_at	Lightblue	J
HSPA1A	200799_at	Brown	I
TEGT	200803_s_at	Hunter	H
TEGT	200804_at	Hunter	H
RPL12	200809_x_at	Hunter	H
RPS10	200817_x_at	Peach	C
ATP5O	200818_at	Lime	D
RPL29	200823_x_at	Hunter	H
SNRPD2	200826_at	Purple	E
PRDX6	200844_s_at	Lime	D
H2AFZ	200853_at	Purple	E
RPS8	200858_s_at	Purple	E
PSAP	200866_s_at	Hunter	H
PSAP	200871_s_at	Hunter	H
S100A10	200872_at	Green	B
DNAJA1	200880_at	Purple	E
RPL23	200888_s_at	Purple	E
SSR1	200891_s_at	Peach	C
SFRS10	200893_at	Hunter	H
MGEA5	200899_s_at	Hunter	H
HLA-E	200904_at	Olive	G
HLA-E	200905_x_at	Hunter	H
EIF4A2	200912_s_at	Hunter	H
TAGLN2	200916_at	Hunter	H
PHC2	200919_at	Brown	I

BTG1	200920_s_at	Peach	C
BTG1	200921_s_at	Peach	C
COX6A1	200925_at	Peach	C
DEK	200934_at	Purple	E
RPL5	200937_s_at	Purple	E
ATP6V0C	200954_at	Peach	C
SDCBP	200958_s_at	Lightblue	J
RPL31	200963_x_at	Purple	E
PPIB	200967_at	Hunter	H
PPT1	200975_at	Hunter	H
GNAS	200981_x_at	Purple	E
HIF1A	200989_at	Hunter	H
ACTR3	200996_at	Purple	E
SSR4	201004_at	Olive	G
TXNIP	201008_s_at	Hunter	H
TXNIP	201010_s_at	Hunter	H
ANXA1	201012_at	Purple	E
LDHB	201030_x_at	Olive	G
HNRNPH1	201031_s_at	Hunter	H
RPLP0	201033_x_at	Peach	C
ADD3	201034_at	Lime	D
DUSP1	201041_s_at	Lightblue	J
PSMF1	201052_s_at	Peach	C
SF3B1	201071_x_at	Purple	E
BCLAF1	201084_s_at	Purple	E
ATP6V1B2	201089_at	Lightblue	J
LGALS1	201105_at	Green	B
PGD	201118_at	Olive	G
EIF5A	201123_s_at	Peach	C
COX7C	201134_x_at	Purple	E
MBNL1	201152_s_at	Purple	E
MBNL1	201153_s_at	Purple	E
CSDA	201160_s_at	Peach	C
CSDA	201161_s_at	Peach	C
ATP6V0E1	201172_x_at	Olive	G
FBXO7	201178_at	Peach	C
DDX3X	201210_at	Purple	E
RPL3	201217_x_at	Peach	C
CAPZA2	201238_s_at	Purple	E
RAF1	201244_s_at	Lightblue	J
CDIPT	201253_s_at	Lime	D
RPS6	201254_x_at	Peach	C
RPS3A	201257_x_at	Purple	E
RPS16	201258_at	Hunter	H
MKRN1	201285_at	Blue	A
PPIA	201293_x_at	Peach	C
ANP32B	201305_x_at	Olive	G
ANP32B	201306_s_at	Olive	G
SH3BGRL	201312_s_at	Peach	C
IFITM2	201315_x_at	Olive	G

STAT6	201331_s_at	Hunter	H
GTF3A	201338_x_at	Hunter	H
FLOT2	201350_at	Brown	I
CST3	201360_at	Green	B
ZFP36L2	201367_s_at	Peach	C
IGF2R	201393_s_at	Brown	I
RPL36A	201406_at	Purple	E
LRP10	201412_at	Brown	I
IFI30	201422_at	Olive	G
CAT	201432_at	Red	K
TALDO1	201463_s_at	Brown	I
EIF4A1	201530_x_at	Green	B
ID2	201565_s_at	Brown	I
ANXA2	201590_x_at	Green	B
EIF3H	201592_at	Olive	G
IFITM1	201601_x_at	Hunter	H
PPP1R12A	201603_at	Purple	E
IFNGR2	201642_at	Brown	I
JAK1	201648_at	Green	B
RPS17	201665_x_at	Purple	E
CCND3	201700_at	Purple	E
LAPTM5	201720_s_at	Hunter	H
CD14	201743_at	Olive	G
ADD3	201752_s_at	Olive	G
ADD3	201753_s_at	Olive	G
RNF13	201779_s_at	Brown	I
ADAR	201786_s_at	Brown	I
LBR	201795_at	Purple	E
TOMM7	201812_s_at	Purple	E
SRGN	201858_s_at	Pink	F
SRGN	201859_at	Pink	F
LRRFIP1	201862_s_at	Purple	E
GSPT1	201912_s_at	Peach	C
LOC552891	201921_at	Lightblue	J
TINP1	201922_at	Hunter	H
ACSL1	201963_at	Lightblue	J
DYNLT1	201999_s_at	Pink	F
EIF1	202021_x_at	Hunter	H
RPL38	202029_x_at	Peach	C
BIRC2	202076_at	Purple	E
IER2	202081_at	Olive	G
SEC14L1	202084_s_at	Brown	I
TSPO	202096_s_at	Olive	G
CUGBP2	202157_s_at	Green	B
BLVRB	202201_at	Peach	C
VASP	202205_at	Olive	G
EIF3M	202231_at	Brown	I
N4BP2L2	202258_s_at	Purple	E
CTSH	202295_s_at	Green	B
RAP1A	202362_at	Hunter	H

NKTR	202379_s_at	Olive	G
RGS2	202388_at	Lightblue	J
BASP1	202391_at	Brown	I
TNFAIP2	202510_s_at	Brown	I
IRF1	202531_at	Brown	I
202603_at	202603_at	Purple	E
GNAQ	202615_at	Olive	G
LYN	202625_at	Lightblue	J
LYN	202626_s_at	Brown	I
RPS19	202649_x_at	Hunter	H
WIPF1	202664_at	Purple	E
TNFSF10	202688_at	Pink	F
COX4I1	202698_x_at	Hunter	H
IFNGR1	202727_s_at	Pink	F
PRKACB	202741_at	Lime	D
ITM2A	202747_s_at	Olive	G
ITGB2	202803_s_at	Hunter	H
SERPINA1	202833_s_at	Brown	I
CD93	202878_s_at	Brown	I
CTSS	202902_s_at	Pink	F
CD97	202910_s_at	Brown	I
S100A8	202917_s_at	Pink	F
GYPC	202947_s_at	Lime	D
HCLS1	202957_at	Olive	G
CYBA	203028_s_at	Hunter	H
RPL27A	203034_s_at	Peach	C
GALNAC4S-6ST	203066_at	Brown	I
EEF1D	203113_s_at	Purple	E
BCL6	203140_at	Lightblue	J
RHOG	203175_at	Hunter	H
RASSF2	203185_at	Lightblue	J
AP1S2	203300_x_at	Peach	C
ARRB2	203388_at	Hunter	H
CTBP1	203392_s_at	Peach	C
PSMA4	203396_at	Purple	E
SATB1	203408_s_at	Pink	F
CD53	203416_at	Hunter	H
FAM8A1	203420_at	Olive	G
SAT1	203455_s_at	Pink	F
SORL1	203509_at	Brown	I
LYST	203518_at	Pink	F
LSP1	203523_at	Hunter	H
S100A9	203535_at	Pink	F
FCGR2A	203561_at	Lightblue	J
CSF3R	203591_s_at	Brown	I
PI3	203691_at	Olive	G
JUND	203752_s_at	Peach	C
GCA	203765_at	Lightblue	J
IL32	203828_s_at	Olive	G
PIK3CD	203879_at	Olive	G

CYBB	203923_s_at	Hunter	H
HLA-DMB	203932_at	Peach	C
CEBPD	203973_s_at	Brown	I
FCGR3B	204006_s_at	Brown	I
FCGR3B	204007_at	Olive	G
PCBP2	204031_s_at	Purple	E
NRGN	204081_at	Peach	C
EEF2	204102_s_at	Hunter	H
CD48	204118_at	Purple	E
TYROBP	204122_at	Brown	I
IMPDH1	204169_at	Brown	I
ALOX5AP	204174_at	Olive	G
GMPR	204187_at	Peach	C
BACH1	204194_at	Lightblue	J
GMFG	204220_at	Pink	F
GLIPR1	204221_x_at	Hunter	H
FCER1G	204232_at	Olive	G
GPSM3	204265_s_at	Purple	E
PSMB9	204279_at	Hunter	H
RGS19	204336_s_at	Hunter	H
S100P	204351_at	Olive	G
ALOX5	204446_s_at	Lightblue	J
EPB49	204505_s_at	Peach	C
SELL	204563_at	Olive	G
VCAN	204620_s_at	Hunter	H
CCL5	204655_at	Hunter	H
CD52	204661_at	Purple	E
RNF24	204669_s_at	Brown	I
HLA-DRB5	204670_x_at	Peach	C
IFIT3	204747_at	Hunter	H
EVI2A	204774_at	Purple	E
HLA-F	204806_x_at	Hunter	H
FGL2	204834_at	Pink	F
LCK	204891_s_at	Brown	I
TLR2	204924_at	Brown	I
ICAM3	204949_at	Olive	G
MNDA	204959_at	Lightblue	J
PTPRCAP	204960_at	Olive	G
NCF1	204961_s_at	Olive	G
CSTA	204971_at	Pink	F
HAGH	205012_s_at	Lime	D
DEFA1	205033_s_at	Purple	E
CCR1	205098_at	Olive	G
CCR1	205099_s_at	Hunter	H
FPR1	205119_s_at	Lightblue	J
NCF4	205147_x_at	Lightblue	J
CSF2RB	205159_at	Lightblue	J
ADAM8	205180_s_at	Lightblue	J
GPR109B	205220_at	Lightblue	J
FCN1	205237_at	Olive	G

TCF7	205255_x_at	Olive	G
GPR183	205419_at	Olive	G
GZMA	205488_at	Purple	E
AQP9	205568_at	Lightblue	J
RASGRP1	205590_at	Hunter	H
CD8A	205758_at	Brown	I
ZC3H11A	205788_s_at	Purple	E
IL7R	205798_at	Olive	G
CD2	205831_at	Olive	G
S100A12	205863_at	Pink	F
ADD3	205882_x_at	Olive	G
CX3CR1	205898_at	Green	B
VNN2	205922_at	Lightblue	J
CREB5	205931_s_at	Brown	I
HIST1H4C	205967_at	Peach	C
AATK	205986_at	Lightblue	J
RNASE2	206111_at	Red	K
CLC	206207_at	Red	K
TNFRSF10C	206222_at	Brown	I
NUDT4	206302_s_at	Blue	A
IFI16	206332_s_at	Olive	G
CCR7	206337_at	Brown	I
CFP	206380_s_at	Hunter	H
PF4	206390_x_at	Peach	C
CYP4F3	206515_at	Brown	I
EEF1A1	206559_x_at	Peach	C
GLRX	206662_at	Purple	E
GZMK	206666_at	Lime	D
PTPN6	206687_s_at	Hunter	H
FAM65B	206707_x_at	Olive	G
LPAR2	206723_s_at	Olive	G
KCNJ2	206765_at	Lightblue	J
HBD	206834_at	Peach	C
IL8RB	207008_at	Brown	I
IL18RAP	207072_at	Olive	G
IL8RA	207094_at	Lightblue	J
PFDN5	207132_x_at	Purple	E
GNG5	207157_s_at	Hunter	H
PTPRC	207238_s_at	Hunter	H
CALM2	207243_s_at	Peach	C
ACSL1	207275_s_at	Lightblue	J
LTB	207339_s_at	Peach	C
ATP5L	207573_x_at	Purple	E
RPL36AL	207585_s_at	Hunter	H
TNFRSF1A	207643_s_at	Lightblue	J
MAP2K3	207667_s_at	Peach	C
NCF4	207677_s_at	Lightblue	J
HINT1	207721_x_at	Purple	E
HUWE1	207783_x_at	Peach	C
RNF10	207801_s_at	Peach	C

SNCA	207827_x_at	Peach	C
LILRA2	207857_at	Brown	I
MMP25	207890_s_at	Brown	I
RBM39	207941_s_at	Purple	E
CD8B	207979_s_at	Brown	I
ARPC2	207988_s_at	Olive	G
HCK	208018_s_at	Lightblue	J
PABPC3	208113_x_at	Olive	G
FKBP8	208255_s_at	Peach	C
TNFAIP8	208296_x_at	Hunter	H
CAPZA1	208374_s_at	Purple	E
CD164	208405_s_at	Purple	E
FGR	208438_s_at	Brown	I
BTF3	208517_x_at	Hunter	H
S100A11P	208540_x_at	Hunter	H
PTMAP7	208549_x_at	Hunter	H
PTP4A2	208616_s_at	Green	B
YBX1	208628_s_at	Lime	D
ACTN1	208636_at	Olive	G
RAC1	208641_s_at	Hunter	H
RPS14	208646_at	Olive	G
CCNI	208656_s_at	Purple	E
CLIC1	208659_at	Pink	F
HMG2	208668_x_at	Peach	C
SFRS3	208672_s_at	Lime	D
ARPC2	208679_s_at	Olive	G
CAPN2	208683_at	Purple	E
HSPA8	208687_x_at	Hunter	H
RPS3	208692_at	Peach	C
EIF3E	208697_s_at	Lime	D
TKT	208699_x_at	Hunter	H
TKT	208700_s_at	Hunter	H
RBM39	208720_s_at	Purple	E
ATP6V1G1	208737_at	Purple	E
ATP5L	208746_x_at	Purple	E
NAP1L1	208752_x_at	Olive	G
H3F3A	208755_x_at	Hunter	H
TSC22D3	208763_s_at	Brown	I
RPL22	208768_x_at	Hunter	H
LTA4H	208771_s_at	Hunter	H
CD46	208783_s_at	Olive	G
ELOVL5	208788_at	Olive	G
PSMA6	208805_at	Purple	E
HINT1	208826_x_at	Purple	E
TAPBP	208829_at	Hunter	H
RPLP0	208856_x_at	Peach	C
ATP5C1	208870_x_at	Purple	E
LCP1	208885_at	Olive	G
DUSP6	208891_at	Hunter	H
HLA-DRA	208894_at	Peach	C

NADK	208918_s_at	Brown	I
NADK	208919_s_at	Brown	I
RPL13	208929_x_at	Peach	C
TGFBR2	208944_at	Olive	G
IFI16	208966_x_at	Olive	G
PECAM1	208982_at	Brown	I
STAT3	208991_at	Olive	G
UCP2	208998_at	Lime	D
FBXL5	209004_s_at	Pink	F
C1orf63	209007_s_at	Purple	E
STAG2	209022_at	Purple	E
GABARAPL2	209046_s_at	Hunter	H
H3F3B	209069_s_at	Olive	G
CORO1A	209083_at	Hunter	H
TUBA1A	209118_s_at	Brown	I
MYD88	209124_at	Brown	I
RPS6	209134_s_at	Peach	C
IGL@	209138_x_at	Blue	A
MBOAT7	209179_s_at	Brown	I
CXCR4	209201_x_at	Hunter	H
WDR45	209216_at	Lime	D
OGT	209240_at	Purple	E
TUBA1C	209251_x_at	Olive	G
HIGD2A	209329_x_at	Hunter	H
CHI3L1	209395_at	Hunter	H
CHI3L1	209396_s_at	Hunter	H
TXNDC1	209476_at	Purple	E
TRAC	209670_at	Olive	G
TRA@	209671_x_at	Hunter	H
CLEC2B	209732_at	Purple	E
HIST1H2BK	209806_at	Peach	C
TRGV9	209813_x_at	Hunter	H
FAM65B	209829_at	Hunter	H
FRAT2	209864_at	Lightblue	J
SELPLG	209879_at	Olive	G
AIF1	209901_x_at	Hunter	H
NFE2	209930_s_at	Olive	G
CD300A	209933_s_at	Brown	I
NCF2	209949_at	Lightblue	J
CASP1	209970_x_at	Pink	F
TCL1A	209995_s_at	Green	B
CD247	210031_at	Hunter	H
LYL1	210044_s_at	Lime	D
KCNJ15	210119_at	Lightblue	J
MBP	210136_at	Hunter	H
CST7	210140_at	Hunter	H
GZMB	210164_at	Peach	C
ITGAX	210184_at	Lightblue	J
HSP90AA1	210211_s_at	Lime	D
ST20	210242_x_at	Lightblue	J

TNFAIP8	210260_s_at	Hunter	H
MS4A1	210356_x_at	Olive	G
MYL4	210395_x_at	Peach	C
SLC11A1	210423_s_at	Brown	I
ANXA2	210427_x_at	Green	B
ATP5L	210453_x_at	Purple	E
SAT1	210592_s_at	Pink	F
LST1	210629_x_at	Brown	I
RPL13A	210646_x_at	Peach	C
SNX3	210648_x_at	Blue	A
USP15	210681_s_at	Olive	G
RNF24	210706_s_at	Brown	I
LYN	210754_s_at	Brown	I
NCOA4	210774_s_at	Pink	F
C1orf38	210785_s_at	Brown	I
APOBEC3A	210873_x_at	Olive	G
PDCD10	210907_s_at	Purple	E
PFDN5	210908_s_at	Purple	E
IL23A	210915_x_at	Hunter	H
TRA@	210972_x_at	Hunter	H
TAGLN2	210978_s_at	Hunter	H
FCGR2C	210992_x_at	Lightblue	J
RPL3	211073_x_at	Peach	C
TARP	211144_x_at	Hunter	H
TNFRSF10C	211163_s_at	Brown	I
SF3B1	211185_s_at	Purple	E
EEF1G	211345_x_at	Peach	C
CASP1	211366_x_at	Pink	F
CASP1	211368_s_at	Pink	F
PPIA	211378_x_at	Peach	C
FCGR2C	211395_x_at	Lightblue	J
SERPINA1	211429_s_at	Brown	I
IGHG3	211430_s_at	Blue	A
NACAP1	211445_x_at	Olive	G
LRRFIP1	211452_x_at	Purple	E
BAG1	211475_s_at	Lime	D
RPS17	211487_x_at	Purple	E
RPS10	211542_x_at	Peach	C
SNCA	211546_x_at	Peach	C
LST1	211581_x_at	Brown	I
LST1	211582_x_at	Brown	I
PTPRO	211600_at	Purple	E
FTHP1	211628_x_at	Olive	G
IGKC	211643_x_at	Blue	A
IGKC	211644_x_at	Blue	A
211645_x_at	211645_x_at	Blue	A
PTAFR	211661_x_at	Hunter	H
IFNGR1	211676_s_at	Pink	F
RPL4	211710_x_at	Purple	E
RPLP0	211720_x_at	Peach	C

POLR2L	211730_s_at	Peach	C
FCER1A	211734_s_at	Peach	C
EVI2B	211742_s_at	Brown	I
TUBA1C	211750_x_at	Olive	G
ATP5F1	211755_s_at	Lime	D
PPIA	211765_x_at	Peach	C
211781_x_at	211781_x_at	Purple	E
EIF4A1	211787_s_at	Green	B
IL23A	211796_s_at	Hunter	H
TRA@	211902_x_at	Hunter	H
CXCR4	211919_s_at	Hunter	H
PTMA	211921_x_at	Hunter	H
BTF3	211939_x_at	Hunter	H
ITGB1	211945_s_at	Purple	E
ARPC5	211963_s_at	Olive	G
HSP90AA1	211969_at	Lime	D
RPLP0	211972_x_at	Peach	C
PPIA	211978_x_at	Peach	C
XPO6	211982_x_at	Lightblue	J
H3F3B	211997_x_at	Olive	G
H3F3A	211999_at	Lightblue	J
RPL3	212039_x_at	Peach	C
ATP6V0D1	212041_at	Hunter	H
RPL7	212042_x_at	Purple	E
MYL6	212082_s_at	Purple	E
SLC25A6	212085_at	Hunter	H
EIF1	212130_x_at	Hunter	H
KCTD12	212192_at	Peach	C
IFITM3	212203_x_at	Brown	I
IDS	212221_x_at	Olive	G
EIF1	212227_x_at	Hunter	H
RPL17	212270_x_at	Purple	E
GNAS	212273_x_at	Purple	E
TPT1	212284_x_at	Peach	C
BCL2L1	212312_at	Peach	C
RBL2	212331_at	Hunter	H
RPS3A	212391_x_at	Purple	E
HNRPDL	212454_x_at	Purple	E
CEBPB	212501_at	Brown	I
PICALM	212506_at	Lightblue	J
DDX3X	212515_s_at	Hunter	H
RPL17	212537_x_at	Purple	E
CDC34	212540_at	Peach	C
SORL1	212560_at	Lightblue	J
DENND5A	212561_at	Lightblue	J
SMCHD1	212569_at	Olive	G
SMCHD1	212577_at	Olive	G
LOC402057	212578_x_at	Purple	E
OSBPL8	212582_at	Hunter	H
OSBPL8	212585_at	Purple	E

PTPRC	212588_at	Hunter	H
IGJ	212592_at	Blue	A
HNRNPC	212626_x_at	Purple	E
TUBA1B	212639_x_at	Olive	G
PPIA	212661_x_at	Peach	C
PAPOLA	212718_at	Purple	E
RPL13A	212790_x_at	Peach	C
SLC25A6	212826_s_at	Hunter	H
IGHM	212827_at	Green	B
MEGF9	212830_at	Lightblue	J
SUB1	212857_x_at	Purple	E
ZDHHC18	212860_at	Lightblue	J
CTBP1	212863_x_at	Peach	C
TPT1	212869_x_at	Peach	C
DCP2	212919_at	Purple	E
NAP1L1	212967_x_at	Olive	G
LOC100133484	212999_x_at	Hunter	H
ABHD3	213017_at	Hunter	H
ARHGEF18	213039_at	Peach	C
ROCK1	213044_at	Purple	E
SET	213048_s_at	Olive	G
ACTR3	213101_s_at	Purple	E
IL23A	213193_x_at	Hunter	H
PLXNC1	213241_at	Lightblue	J
LOC100128836	213356_x_at	Olive	G
ATP5C1	213366_x_at	Purple	E
HSPA6	213418_at	Lightblue	J
EEF1A1	213477_x_at	Peach	C
ANXA2	213503_x_at	Green	B
CD3D	213539_at	Hunter	H
LDHB	213564_x_at	Olive	G
RPL14	213588_x_at	Hunter	H
HNRNPH1	213619_at	Pink	F
C17orf72	213620_s_at	Olive	G
ASAH1	213702_x_at	Pink	F
MYO1F	213733_at	Brown	I
ATP5A1	213738_s_at	Hunter	H
CAP1	213798_s_at	Olive	G
RPSA	213801_x_at	Peach	C
CAMKK2	213812_s_at	Hunter	H
H3F3A	213828_x_at	Hunter	H
HLA-DQA1	213831_at	Hunter	H
NAP1L1	213864_s_at	Olive	G
SUMO2	213881_x_at	Hunter	H
LOC100133233	213888_s_at	Olive	G
NKG7	213915_at	Hunter	H
RPS7	213941_x_at	Purple	E
LYZ	213975_s_at	Hunter	H
SAT1	213988_s_at	Olive	G
RPL22	214042_s_at	Brown	I

NCF1B	214084_x_at	Olive	G
GLIPR1	214085_x_at	Hunter	H
ATP6V0E1	214150_x_at	Olive	G
RPLP0-like	214167_s_at	Purple	E
LST1	214181_x_at	Brown	I
RPL12	214271_x_at	Hunter	H
HIST2H2AA3	214290_s_at	Olive	G
RPS9	214317_x_at	Hunter	H
TPT1	214327_x_at	Peach	C
HSP90AA1	214328_s_at	Lime	D
MATR3	214363_s_at	Lime	D
EEF1D	214394_x_at	Purple	E
KLRB1	214470_at	Purple	E
SUB1	214512_s_at	Purple	E
GNAS	214548_x_at	Purple	E
LST1	214574_x_at	Brown	I
IGKC	214669_x_at	Blue	A
IGLJ3	214677_x_at	Blue	A
HNRNPC	214737_x_at	Purple	E
XPO6	214784_x_at	Lightblue	J
BTF3	214800_x_at	Hunter	H
IGKC	214836_x_at	Blue	A
GLUL	215001_s_at	Olive	G
TRIM58	215047_at	Peach	C
AIF1	215051_x_at	Hunter	H
HIST1H2AC	215071_s_at	Hunter	H
GTF3A	215091_s_at	Hunter	H
IGL@	215121_x_at	Blue	A
NTN2L	215176_x_at	Blue	A
SOD2	215223_s_at	Lightblue	J
IGL@	215379_x_at	Blue	A
GSPT1	215438_x_at	Peach	C
MAP2K3	215498_s_at	Peach	C
MAP2K3	215499_at	Peach	C
TRAV20	215524_x_at	Hunter	H
LST1	215633_x_at	Brown	I
ASCC2	215684_s_at	Peach	C
PABPC1	215823_x_at	Olive	G
ADFP	215895_x_at	Purple	E
IGLL3	215946_x_at	Blue	A
LOC642741	215963_x_at	Peach	C
LOC152719	215978_x_at	Purple	E
IGKV1D-13	216207_x_at	Blue	A
LOC100128140	216342_x_at	Hunter	H
RPS17L4	216348_at	Purple	E
LOC728453	216380_x_at	Hunter	H
PTMAP4	216384_x_at	Hunter	H
LOC652493	216401_x_at	Blue	A
PTMAP5	216515_x_at	Olive	G
TPT1	216520_s_at	Peach	C

LOC100131713	216570_x_at	Olive	G
LOC146053	216823_at	Purple	E
TARP	216920_s_at	Hunter	H
CKAP2	216984_x_at	Blue	A
IGHG1	217022_s_at	Blue	A
CXCR4	217028_at	Green	B
CD300A	217078_s_at	Hunter	H
LOC100127893	217092_x_at	Purple	E
TRD@	217143_s_at	Hunter	H
IGL@	217148_x_at	Blue	A
IGKC	217157_x_at	Blue	A
LOC100130100	217378_x_at	Blue	A
MS4A1	217418_x_at	Olive	G
HLA-J	217436_x_at	Hunter	H
LOC339562	217480_x_at	Blue	A
COX7C	217491_x_at	Purple	E
GNAS	217673_x_at	Purple	E
YWHAB	217717_s_at	Purple	E
EIF3EIP	217719_at	Olive	G
CHCHD2	217720_at	Peach	C
S100A6	217728_at	Olive	G
ITM2B	217731_s_at	Olive	G
ITM2B	217732_s_at	Olive	G
NAMPT	217738_at	Lightblue	J
NAMPT	217739_s_at	Lightblue	J
RPL7A	217740_x_at	Peach	C
ADIPOR1	217748_at	Peach	C
RAB31	217762_s_at	Olive	G
NDUFA4	217773_s_at	Purple	E
PNRC2	217779_s_at	Purple	E
PRR13	217794_at	Olive	G
ATP5E	217801_at	Peach	C
C20orf24	217835_x_at	Brown	I
RNF130	217865_at	Brown	I
METTL9	217868_s_at	Peach	C
FAM49B	217916_s_at	Olive	G
CMTM6	217947_at	Brown	I
NOLA3	217962_at	Olive	G
FAM129A	217966_s_at	Brown	I
FAM129A	217967_s_at	Lightblue	J
SEPX1	217977_at	Lightblue	J
RNASET2	217983_s_at	Olive	G
RNASET2	217984_at	Olive	G
HSD17B11	217989_at	Brown	I
EFHD2	217992_s_at	Brown	I
PRPF40A	218053_at	Peach	C
ARGLU1	218067_s_at	Purple	E
FXYD5	218084_x_at	Hunter	H
SLC25A37	218136_s_at	Olive	G
NAGK	218231_at	Hunter	H

PRICKLE4	218233_s_at	Hunter	H
FLJ22662	218454_at	Brown	I
P2RY5	218589_at	Purple	E
C12orf35	218614_at	Olive	G
GIMAP5	218805_at	Brown	I
TESC	218872_at	Lime	D
PLAC8	219014_at	Hunter	H
CKLF	219161_s_at	Pink	F
KLF2	219371_s_at	Peach	C
TREM1	219434_at	Brown	I
DPEP2	219452_at	Olive	G
RTN3	219549_s_at	Lightblue	J
PDZK1IP1	219630_at	Lime	D
MS4A6A	219666_at	Green	B
ERAF	219672_at	Peach	C
RPL36	219762_s_at	Hunter	H
FRAT1	219889_at	Lightblue	J
P2RY13	220005_at	Lightblue	J
C5AR1	220088_at	Brown	I
UBXN6	220757_s_at	Lime	D
HBQ1	220807_at	Peach	C
RPL22	220960_x_at	Hunter	H
TMEM49	220990_s_at	Lightblue	J
CHST6	221059_s_at	Hunter	H
SH3BGRL3	221269_s_at	Peach	C
FFAR2	221345_at	Brown	I
MRLC2	221474_at	Purple	E
RPL15	221475_s_at	Purple	E
221477_s_at	221477_s_at	Lightblue	J
BNIP3L	221478_at	Blue	A
GLS	221510_s_at	Purple	E
LEF1	221558_s_at	Brown	I
FAIM3	221601_s_at	Brown	I
FAIM3	221602_s_at	Hunter	H
IGKC	221651_x_at	Blue	A
IGKC	221671_x_at	Blue	A
NPM1	221691_x_at	Olive	G
CLEC7A	221698_s_at	Brown	I
VCAN	221731_x_at	Hunter	H
C19orf22	221764_at	Peach	C
RPL22	221775_x_at	Hunter	H
CCDC72	221791_s_at	Purple	E
	08-mar 221824_s_at	Peach	C
TNPO1	221829_s_at	Peach	C
HLA-F	221875_x_at	Hunter	H
HSPA8	221891_x_at	Hunter	H
SLC25A37	221920_s_at	Olive	G
GLRX5	221932_s_at	Peach	C
PILRA	222218_s_at	Brown	I
LOC441533	222229_x_at	Purple	E

TUG1	222244_s_at	Hunter	H
RPL18	222297_x_at	Hunter	H
CD52	34210_at	Purple	E
ATP6V0C	36994_at	Peach	C
LRCH4	37796_at	Lime	D
WAS	38964_r_at	Lime	D
TCL1A	39318_at	Green	B
FKBP8	40850_at	Peach	C
	09-set 41220_at	Hunter	H
PI3	41469_at	Olive	G
C19orf22	55705_at	Peach	C
SLC25A37	222528_s_at	Hunter	H
SLC25A37	222529_at	Hunter	H
FLJ11151	222686_s_at	Brown	I
TMBIM4	222845_x_at	Olive	G
SLC38A2	222982_x_at	Purple	E
UBXN6	223012_at	Lime	D
PRELID1	223032_x_at	Green	B
CMTM6	223047_at	Lightblue	J
TMEM14C	223105_s_at	Hunter	H
YPEL3	223179_at	Hunter	H
ALS2CR2	223266_at	Peach	C
MS4A6A	223280_x_at	Hunter	H
RASSF5	223322_at	Peach	C
TNFSF13B	223501_at	Pink	F
TNFSF13B	223502_s_at	Brown	I
SLC25A39	223649_s_at	Peach	C
RGS18	223809_at	Hunter	H
C20orf24	223880_x_at	Brown	I
TMBIM4	223892_s_at	Olive	G
HSPA8	224187_x_at	Hunter	H
MS4A6A	224356_x_at	Hunter	H
ARHGAP9	224451_x_at	Brown	I
MALAT1	224558_s_at	Purple	E
TncRNA	224565_at	Hunter	H
TncRNA	224566_at	Hunter	H
ERGIC1	224576_at	Peach	C
SLC38A1	224579_at	Hunter	H
COTL1	224583_at	Purple	E
SUB1	224586_x_at	Purple	E
224597_at	224597_at	Purple	E
KLF6	224606_at	Brown	I
C20orf108	224690_at	Peach	C
224691_at	224691_at	Purple	E
STT3B	224700_at	Purple	E
CDC42SE2	224709_s_at	Lime	D
C12orf57	224719_s_at	Brown	I
CENPL	224741_x_at	Purple	E
MSL-1	224765_at	Lightblue	J
TRIM25	224806_at	Brown	I

ETS1	224833_at	Olive	G
C20orf199	224915_x_at	Purple	E
TMEM49	224917_at	Pink	F
KIAA1949	224927_at	Purple	E
RAB11FIP1	225177_at	Lightblue	J
RPL35A	225190_x_at	Purple	E
RAB24	225251_at	Lightblue	J
SMAP2	225282_at	Olive	G
COMMD6	225312_at	Purple	E
PTEN	225363_at	Lightblue	J
C10orf54	225373_at	Brown	I
RNF149	225414_at	Lightblue	J
SNHG6	225547_at	Hunter	H
GLIPR2	225602_at	Brown	I
DEF8	225637_at	Olive	G
MYADM	225673_at	Hunter	H
ATG16L2	225883_at	Lightblue	J
LOC100133182	225899_x_at	Lightblue	J
MAP3K1	225927_at	Peach	C
STEAP4	225987_at	Lightblue	J
CD47	226016_at	Olive	G
SLC25A37	226179_at	Lightblue	J
IL7R	226218_at	Hunter	H
C20orf199	226227_x_at	Purple	E
RCAN3	226272_at	Olive	G
MXD1	226275_at	Lightblue	J
226297_at	226297_at	Pink	F
RICTOR	226312_at	Purple	E
CDC42	226400_at	Peach	C
PIK3AP1	226459_at	Pink	F
SON	226465_s_at	Peach	C
LOC283666	226682_at	Lime	D
SLC12A6	226741_at	Brown	I
IFIT2	226757_at	Hunter	H
OGFRL1	226810_at	Olive	G
FAM46C	226811_at	Blue	A
MPEG1	226818_at	Green	B
MPEG1	226841_at	Green	B
FAM101B	226905_at	Peach	C
tcag7.907	227129_x_at	Lightblue	J
227184_at	227184_at	Brown	I
FGL2	227265_at	Olive	G
FYB	227266_s_at	Olive	G
TMC8	227353_at	Hunter	H
LRRFIP1	227391_x_at	Purple	E
STUB1	227625_s_at	Hunter	H
JAK3	227677_at	Olive	G
FGD3	227811_at	Olive	G
PCGF5	227935_s_at	Peach	C
AMICA1	228094_at	Lightblue	J

RICTOR	228248_at	Hunter	H
228498_at	228498_at	Hunter	H
MS4A1	228592_at	Olive	G
SLC6A6	228754_at	Lightblue	J
BCL6	228758_at	Lightblue	J
MXD1	228846_at	Lightblue	J
ATG16L2	229389_at	Hunter	H
IFIT3	229450_at	Hunter	H
TLR8	229560_at	Lightblue	J
LRRK2	229584_at	Pink	F
TAGAP	229723_at	Green	B
229934_at	229934_at	Pink	F
CMTM2	229967_at	Lightblue	J
AP1S2	230264_s_at	Peach	C
230333_at	230333_at	Green	B
TUBB1	230690_at	Peach	C
SORL1	230707_at	Brown	I
APBB1IP	230925_at	Brown	I
231078_at	231078_at	Lime	D
FCRL3	231093_at	Hunter	H
SLC25A37	231274_s_at	Olive	G
ARHGAP9	232543_x_at	Brown	I
CTSS	232617_at	Brown	I
PROK2	232629_at	Lightblue	J
GUSBP1	232889_at	Olive	G
LOC728179	234512_x_at	Olive	G
LOC388474	234873_x_at	Hunter	H
MBNL1	235879_at	Hunter	H
236293_at	236293_at	Olive	G
236439_at	236439_at	Olive	G
MDM4	236814_at	Purple	E
TMEM71	238429_at	Brown	I
CFLAR	239629_at	Olive	G
HBM	240336_at	Peach	C
241435_at	241435_at	Pink	F
242695_at	242695_at	Hunter	H
NAMPT	243296_at	Brown	I
CLEC12A	1552398_a_at	Hunter	H
CSF3R	1553297_a_at	Brown	I
COX1	1553538_s_at	Peach	C
ND2	1553551_s_at	Purple	E
LOC100133315	1553567_s_at	Peach	C
SH3KBP1	1553588_at	Purple	E
PDZK1IP1	1553589_a_at	Lime	D
MED25	1553993_s_at	Hunter	H
FBXO7	1554423_a_at	Peach	C
CARD8	1554479_a_at	Purple	E
FCER1G	1554899_s_at	Olive	G
NAMPT	1555167_s_at	Lightblue	J
ITGB2	1555349_a_at	Hunter	H

HNRNPA3	1555653_at	Purple	E
CCL5	1555759_a_at	Hunter	H
RHOA	1555814_a_at	Hunter	H
HINT1	1555961_a_at	Purple	E

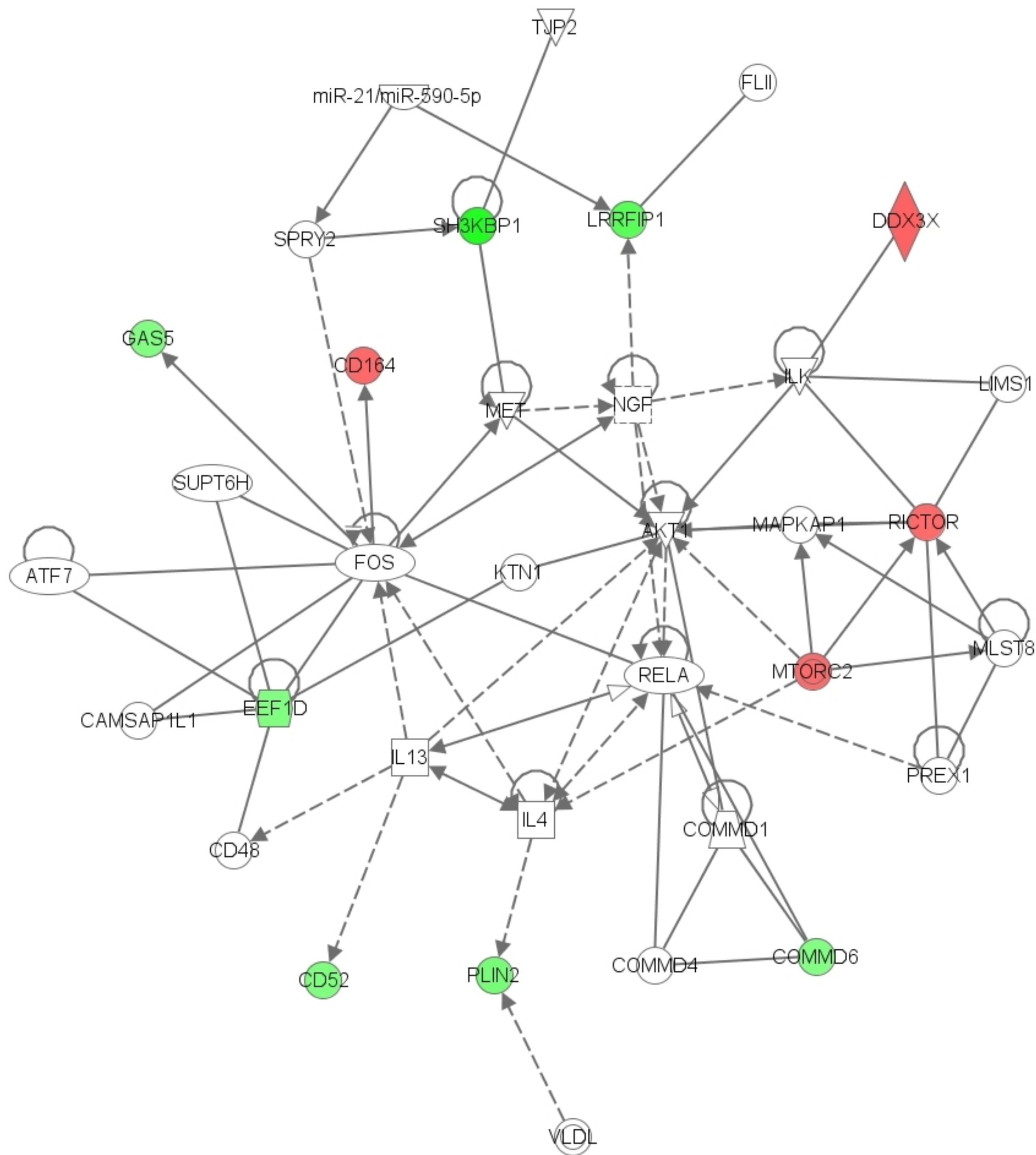


Table S6. Biomarker listing with rows and groups as in Figure 1A dendrogram

Group	Row	Description	Units	Annotation
1	1	Serum Total Globulin	g/dL	
	2	Albumin/Globulin Ratio		
	3	Serum Uric Acid	mg/dL	Body weight, cholesterol, metabolic indicators
	4	Total Cholesterol to High density Lipoprotein Ratio		Body weight, cholesterol, metabolic indicators
	5	Low density Lipoprotein	mg/dL	Body weight, cholesterol, metabolic indicators
	6	Total Cholesterol	mg/dL	Body weight, cholesterol, metabolic indicators
	7	Serum Glucose	mg/dL	Body weight, cholesterol, metabolic indicators
	8	Serum Phospholipids Concentration	Mg/dL	Body weight, cholesterol, metabolic indicators
	9	Serum Unbound Iron-Binding Capacity	ug/dL	Body weight, cholesterol, metabolic indicators
	10	Plasma Leptin	ng/mL	Body weight, cholesterol, metabolic indicators
	11	Blood Pressure Pulse	beats/min	Body weight, cholesterol, metabolic indicators
	12	Subject Weight	kg	Body weight, cholesterol, metabolic indicators
	13	Subject Body Mass Index Weight/height	kg/m ²	Body weight, cholesterol, metabolic indicators
	14	Very Low Density Lipoprotein		Body weight, cholesterol, metabolic indicators
	15	Serum Triglycerides	mg/dL	Body weight, cholesterol, metabolic indicators
2	1	Serum Derm Farin Dustmite	kUA/L	Allergens

	2	Serum Derm Pter Dustmite	kUA/L	Allergens
	3	Phadiatop (10 common allergy screen) [#]	kUA/L	Allergens
	4	Fractional Exhaled Nitric Oxide		
	5	Serum Chloride	mmol/L	
	6	BP Oxygen Saturation (Dissolved Oxygen)	%	
	7	Blood Hemoglobin	g/DdL	
	8	High density Lipoprotein	mg/dL	
	9	Urine Creatinine	mg/dL	
	10	Platelet Count	K/uL	
	11	Serum Creatinine	mg/dL	
	12	Serum Glycated Hemoglobin	%	
	13	Serum Aspartate Aminotranferase (AST) Serum Glutamic-Oxaloacetic Transaminase (SGOT)	IU/L	
	15	Serum Blood Urea Nitrogen	mg/dL	
	16	Serum Total Protein	g/dL	
	17	Mean of first Two Diastolic Blood Pressure Measurements	mmHg	
	18	Serum Ferritin	ng/ml	
	19	Serum Gamma-Glutamyl transpeptidase (GGT)	IU/L	
	20	Serum Lactate Dehydrogenase	IU/L	
	21	Serum Total Bilirubin	mg/dL	
	22	Forced Expiratory Volume 1 ratio to Forced Vital Capacity	%	Lung Function
	23	Forced Expiratory Volume 5 ratio to Forced Vital Capacity	%	Lung Function
	24	Peak Expiratory Flow	L/min	Lung Function
	25	Forced Expiratory Flow Between 25% and 75% of Forced Expiratory Flow		Lung Function
	26	Sodium	mmol/L	
	27	Serum Osmolality	mOsmol/kg	

	28	Serum Calcium	mg/dL	
	29	Albumin	g/dL	
	30	Serum German Cockroach	kUA/L	
	31	Alkaline phosphatase	IU/L	
	32	Serum Total Antioxident Status	mmol/L	
	33	Serum Glutamic Pyruvic Transaminase	IU/L	
	34	Potassium	mmol/L	
	35	Serum Arachidonic Acid	ug/ml	
	36	Serum Phosphorus	mg/dL	
	37	Blood Hematocrit	%	
	38	Subject Height	cm	
	39	Subject Age	Years	
	40	Serum Iron	ug/dl	
	41	C-reactive Protiein	mg/mL	
	42	Total Serum IgE	kU/L	Allergens
	43	FoodScreen (5 common food allergens)	kUA/L	Allergens
	44	Serum Cat Dander Epithel	kUA/L	Allergens
	45	Serum Dog Dander	kUA/L	Allergens
	46	Serum Alternaria Alternata	kUA/L	Allergens
	47	Serum Aspergillus Fumigatus	kUA/L	Allergens
	48	Mean of first two Systolic Blood Pressure Measurements	mmHg	
	49	Red Blood Cell Distribution Width	%	
	50	Serum Rat Urine Protein	kUA/L	Allergens
	51	Serum Mouse Urine Protein	kUA/L	Allergens
	52	Serum Cladosporium Herbarum	kUA/L	Allergens
	53	Serum Penicillium Notatum	kUA/L	Allergens
	54	Basophil percent of sum White Blood Cells	%	
	55	Plasma Average of Reactive Oxygen Species Measurments minus Control	RLU*	
	56	Interleukin-4	pg/ml	

	57	Serum Fibrinogen	mg/dL	
3	1	Mean Corpuscular Volume	fL**	
	2	Mean Corpuscular Hemoglobin	pg	
	3	Red Blood Cell Count	M/uL	Blood cell count
	4	Mean Corpuscular hemoglobin concentration	g/dL	Blood cell count
	5	Eosinophil percent of sum White Blood Cells	%	Blood cell count
	6	Monocyte percent of sum White Blood Cells	%	Blood cell count
4	1	White Blood Cell Count	K/uL	Blood cell count
	2	Neutrophils percent of sum White Blood Cells	%	Blood cell count
	3	Lymphocyte percent of sum White Blood Cells	%	Blood cell count

* relative luminescence unit, ** femtoliters. #Phadiatop is a single analysis that measures the relative level of IgE antibody specific for a panel of 10 common aeroallergens. The Group column is color-coded to match the dendrogram on the Y-axis of Figure 1A; row designates the order of its biomarkers. Annotation column shows the precise biomarkers referenced by the annotations provided on Figure 1A.

