Genome-wide interaction study of dust mite allergen on lung function in children with asthma

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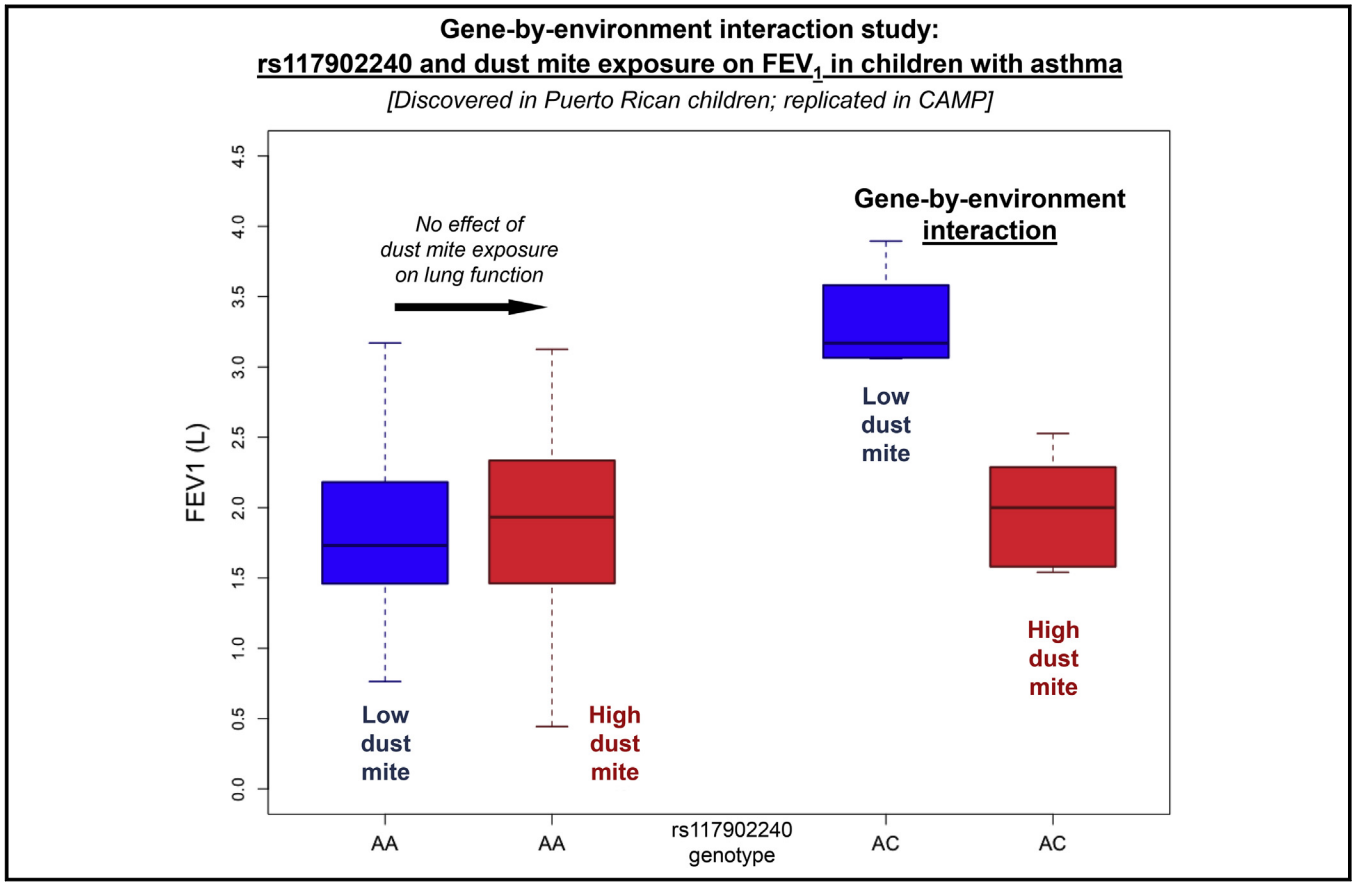
GRAPHICAL ABSTRACT



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Background: Childhood asthma is likely the result of gene-by-environment (G × E) interactions. Dust mite is a known risk factor for asthma morbidity. Yet, there have been no genome-wide G × E studies of dust mite allergen on asthma-related phenotypes.

Objective: We sought to identify genetic variants whose effects on lung function in children with asthma are modified by the level of dust mite allergen exposure.

Methods: A genome-wide interaction analysis of dust mite allergen level and lung function was performed in a cohort of Puerto Rican children with asthma (Puerto Rico Genetics of Asthma and Lifestyle [PRGOAL]). Replication was attempted in 2 independent cohorts, the Childhood Asthma Management Program (CAMP) and the Genetics of Asthma in Costa Rica Study.

Results: Single nucleotide polymorphism (SNP) rs117902240 showed a significant interaction effect on FEV_1 with dust mite allergen level in PRGOAL (interaction $P = 3.1 \times 10^{-8}$), and replicated in the same direction in CAMP white children and CAMP Hispanic children (combined interaction $P = .0065$ for replication cohorts and 7.4×10^{-9} for all cohorts). Rs117902240 was positively associated with FEV_1 in children exposed to low dust mite allergen levels, but negatively associated with FEV_1 in children exposed to high levels. This SNP is on chromosome 8q24, adjacent to a binding site for CCAAT/enhancer-binding protein beta, a transcription factor that forms part of the IL-17 signaling pathway. None of the SNPs identified for FEV_1/forced vital capacity replicated in the independent cohorts.

Conclusions: Dust mite allergen exposure modifies the estimated effect of rs117902240 on FEV_1 in children with asthma. Analysis of existing data suggests that this SNP may have transcription factor regulatory functions. (J Allergy Clin Immunol 2017;140:996-1003.)

Key words: *Childhood asthma, lung function, dust mite allergen, genome-wide interaction study, gene-by-environment interactions, CEBPβ*

Asthma, the most common noncommunicable chronic illness among children,[1] has an estimated heritability of up to 50% to 90%.[2,3] Although dozens of genes that confer susceptibility to asthma or asthma morbidity have been recently identified,[4] single nucleotide polymorphisms (SNPs) in such genes account for as little as 10% to 50% of the disease's heritability. One potential reason for this "missing heritability" is gene-by-environment interactions because certain genetic variants may confer risk only in the presence of certain environmental exposures.

One of the best characterized environmental risk factors for asthma morbidity is exposure to indoor allergens. In particular, dust mite allergen is known to increase the risk of asthma exacerbations, and to increase airway responsiveness while reducing lung function.[5-7] The cysteine proteases in dust mites' fecal particles are potent inducers of allergic sensitization,[8] and exposure to house dust mite can also trigger a direct, nonallergic, inflammatory reaction.[9] Both interventions to reduce dust mite exposure[10,11] and trials of immune therapy to induce dust mite tolerance[12-14] have been shown to improve asthma symptoms or reduce morbidity from asthma.

Few studies have looked at the effect of the interaction between genetic variants and allergens on asthma. Gene-by-allergen interactions have been reported for dust mite and several candidate genes for asthma, including *IL10*,[15] *TGFB1*,[16] or the purinergic receptor P2Y, G-protein coupled 12 (P2RY12).[17] More recently, a study using genome-wide expression *in vitro* responses to dust mite allergen reported that *IL9* may interact with environmental dust mite allergen and increase severe asthma exacerbations.[18] In the present study, we performed a genome-wide interaction study of the effect of house dust mite allergen (*Dermatophagoides pteronyssinus*) level on lung function in Puerto Rican children with asthma, with replication studies in 2 independent cohorts of children with asthma.

Abbreviations used
CAMP: Childhood Asthma Management Program
CEBPβ: CCAAT/enhancer-binding protein beta
FVC: Forced vital capacity
GACRS: Genetics of Asthma in Costa Rica Study
PRGOAL: Puerto Rico Genetics of Asthma and Lifestyle
SNP: Single nucleotide polymorphism

METHODS

Study population

As part of a case-control study of childhood asthma in Puerto Ricans (Puerto Rico Genetics of Asthma and Lifestyle [PRGOAL]), we recruited 618 children with asthma (defined as physician-diagnosed asthma and at least 1 episode of wheeze in the previous year) living in Hartford (Conn) and San Juan (Puerto Rico). The details of subject recruitment have been published previously.[19-21]

In brief, from September 2003 to July 2008, flyers were distributed to all parents of children in grades K-8 in 15 public elementary/middle schools in Hartford, Conn, that enroll a high proportion (42% to 94%) of Puerto Rican children. Of 640 children whose parents were interested in the study, 585 (91.4%) were eligible after screening; parents of 449 (76.7%) of these 585 children (including 267 children with asthma and 182 control subjects) agreed to participate. There were no significant differences in age, sex, or area of residence between eligible children who did (n = 449) and did not (n = 136) participate. From March 2009 to June 2010, children were recruited from households in metropolitan San Juan, Puerto Rico, selected using a multistage probability sample design. Primary sampling units were randomly selected neighborhood clusters based on the 2000 US census, and secondary sampling units were randomly selected households within each primary sampling unit. A household was eligible if 1 or more resident was a child 6 to 14 years old. In households with more than 1 eligible child, 1 child was selected for screening; in households with multiple eligible children, 1 child was randomly selected using Kish tables. Of 6401 contacted households, 1111 had 1 or more child within the study age range who met other inclusion criteria. To reach our target sample size (≥700 children), we attempted to enroll a random sample (n = 783) of these 1111 children. Parents of 105 (13.4%) of these households refused to participate or could not be reached. There were no significant differences in age, sex, or area of residence between eligible children who did (n = 678, including 351 children with asthma and 327 control subjects) and did not (n = 105) participate. At both study sites, participants had to have 4 Puerto Rican grandparents and had to have lived in the same household for 1 or more year. Of the 618 children with asthma at both study sites, 520 (287 from San Juan and 233 from Hartford) had blood samples and sufficient DNA for genome-wide genotyping. Of these 520 children, 440 (84.6%, 249 from San Juan and 191 from Hartford) also had data on indoor dust mite allergen level and lung function, and were thus included in the current analysis.

Ethics statement

Written consent was obtained from parents of participating children, from whom written assent was also obtained. The study was approved by the