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Gene-environment interaction between an *IL4R* variant and school endotoxin exposure contributes to asthma symptoms in inner-city children

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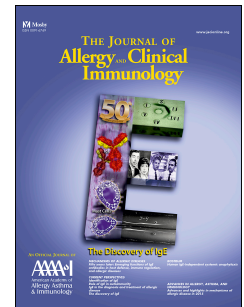
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Title: Gene-environment interaction between an *IL4R* variant and school endotoxin exposure contributes to asthma symptoms in inner-city children

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Capsule summary (30/35 words)

An interleukin 4 receptor genetic variant (IL4R α -Q576R) is common in children of African ancestry.

There is a gene-environment interaction between this variant, school endotoxin exposure, and asthma symptoms.

Key words: asthma; gene-environment interaction; endotoxin; school; health disparities; Q551R; Q576R

Word count: 996/1000

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To the Editor:

Gene-environment interactions are thought to play a critical role in determining asthma incidence and severity. A human interleukin 4 receptor alpha chain gene (*IL4R*) variant that results in a glutamine to arginine substitution at amino acid residue 576 (*IL4R*α-Q576R polymorphism) is associated with asthma diagnosis and severity¹. We have recently shown that the *IL4R*α^{R576} variant promotes severe airway inflammation by uniquely linking the *IL4R* to a growth-factor-receptor-bound protein 2 (GRB2)-dependent intracellular signaling pathway that destabilizes allergen-specific regulatory T cells to drive mixed T_H2/T_H17 cell inflammation². School endotoxin exposure is associated with asthma morbidity³. High endotoxin exposure is associated with increased T_H17 cell skewing⁴, leading us to test the hypothesis that there is an interaction between the *IL4R*α-Q576R polymorphism, school endotoxin exposure, and asthma symptoms.

The School Inner-city Asthma Study (SICAS) is a single-center prospective cohort study conducted between 2008 and 2013 of children with persistent asthma attending inner-city elementary schools in a northeastern United States city (**Online Repository**). Repeated assessment of asthma symptom days over a 14-day period was assessed by parental or caretaker survey at three month intervals. One-week classroom air samples were collected twice during the school year using charged particle samplers (Quadra; Sharper Image/Camelot Venture Group); endotoxin levels were assessed using the Limulus Amebocyte Lysate assay³. Genotyping of the *IL4R*^{Q576} and *IL4R*^{R576} alleles was carried out using the amplification resistance mutation screen PCR method² on DNA was extracted from either whole blood (Gentra Puregene Blood Kit; Qiagen) or saliva (prepIT L2P; DNA Genotek).

The *IL4R*α-Q576R genotypes were modeled as a three-group categorical variable (*Q/Q*, *Q/R*, or *R/R* genotypes, with the *Q/Q* genotype as the reference group). To test the hypothesis that the genotypes

differed by self-reported race, Fisher's exact tests were performed. To test the hypothesis that a gene-environment interaction was present, a multiplicative term between classroom endotoxin levels (continuous) and genotype (3-level categorical variable) was included in binomial family generalized estimating equations with a logit link and an overdispersion parameter. These models included only observations during the school year, and adjusted for age, gender, self-reported race, allergic sensitization, baseline asthma severity, use of asthma controller medications, annual income, and season (using linear and quadratic terms for days since school start). All statistical analyses were performed in Stata version 13.1 (StataCorp). Two-sided p-values of <0.05 were considered statistically significant for main effects; p-values of <0.10 were considered statistically significant for interactions.

Baseline characteristics of the 236 children included in the analysis are depicted in **Table 1**; 51.7% were male, the average age was 8.0 ± 1.9 years, and 5.1% self-identified as being Caucasian. The distribution of genotypes differed by race; 75.0%, 13.1%, and 31.7% of Caucasian, African-American, and Hispanic children had the *Q/Q* genotype, whereas 0%, 47.6%, and 14.6% of Caucasian, African-American, and Hispanic children had the *R/R* genotype ($p < 0.001$). The frequency of the *Q* allele was highest in children of Caucasian race, whereas the frequency of the *R* allele was the highest in children of African-American or mixed race (**Supplementary Table 1**). Median measured classroom endotoxin levels were 27.5 EU/m^3 [interquartile range $7.4 - 71.8 \text{ EU/m}^3$]. In univariate analyses, the main effects of the genotype and of classroom endotoxin levels on asthma symptoms did not reach statistical significance. In a multivariate model, the effect of classroom endotoxin levels on asthma symptom days varied by genotype (overall interaction p-value = 0.09; pairwise interaction p-values for *Q/R* vs. *Q/Q* = 0.115, *R/R* vs. *Q/Q* = 0.049). Higher classroom endotoxin levels were associated with fewer asthma symptoms for children with the *Q/Q* genotype (OR 0.76 [0.55 – 1.04]), an equivocal effect for the *Q/R* genotype (OR 1.10 [0.78 - 1.55]), and increased asthma symptoms for the *R/R* genotype (OR 1.34 [0.85 - 2.13], **Figure 1, Supplementary Table 2**).

100 In this study, we identify a gene-environment interaction associated with pediatric asthma symptoms. Few
101 gene-environment interaction studies involving the IL4R α -Q576R polymorphism have been performed.

102 In a humanized mouse model of the IL4R α -R576 variant (*Il4ra*^{R576} mice), exposure of the mice to fine
103 and ultrafine particles from vehicular exhaust exacerbated allergic inflammation in association with
104 augmented mixed Th2/Th17 airway cell responses⁵, demonstrating the plausibility that interactions
105 between this allele and environmental exposures contribute to asthma morbidity. Similarly, an
106 exaggerated mixed Th2-Th17 cell inflammation may underlie the interaction between the IL4R α -R576
107 variant and endotoxin exposure.

108 Of note, high endotoxin exposure in the presence of the Q/Q genotype was associated with a protective
109 effect against asthma symptoms. A pro-con effect of endotoxin exposure on asthma has been well
110 described in epidemiologic studies. For example, Tischer *et al*⁶, in an analysis of three large European
111 birth cohorts, reported a protective effect of early life endotoxin exposure on later asthma development in
112 the Spanish cohort, an equivocal effect in the German cohort, and a harmful effect in the Dutch cohort.
113 Our findings support the possibility that the *IL4R* Q versus R variants influence the outcome of endotoxin
114 exposure on asthma.

115 Our study has a few limitations. Our sample size was modest, thus we had limited power to detect
116 associations, and we were not able to account for possible confounding due to population stratification by
117 performing stratified analyses using self-reported race. We did not validate our findings in an independent
118 cohort, and there is linkage disequilibrium between the polymorphism studied and other *IL4R*
119 polymorphisms; thus, our findings are preliminary and would need to be verified in larger studies.

120 However, it has been suggested that gene-environment interactions contribute to racial disparities in
121 asthma outcomes⁷. United States poverty rates are highest in ethnic minorities⁸; a prior nationwide study
122 found that poverty is associated with higher home endotoxin exposure⁹. It is possible that the gene-
123 environment interaction we observed contributes to racial disparities in pediatric asthma. While it may be
124 difficult to address individual home environmental conditions, a public health initiative addressing the

125 environment of inner-city schools, where there is a high proportion of ethnic minorities, may improve
126 observed disparities in asthma.

REFERENCES CITED

1. Rosa-Rosa L, Zimmermann N, Bernstein JA, Rothenberg ME, Khurana Hershey GK. The R576 IL-4 receptor alpha allele correlates with asthma severity. *J Allergy Clin Immunol*. 1999;104(5):1008-14.
2. Massoud AH, Charbonnier LM, Lopez D, Pellegrini M, Phipatanakul W, Chatila TA. An asthma-associated IL4R variant exacerbates airway inflammation by promoting conversion of regulatory T cells to TH17-like cells. *Nat Med*. 2016;22(9):1013-22.
3. Lai PS, Sheehan WJ, Gaffin JM, Petty CR, Coull BA, Gold DR, Phipatanakul W. School Endotoxin Exposure and Asthma Morbidity in Inner-city Children. *Chest*. 2015;148(5):1251-8.
4. Glader P, Smith ME, Malmhall C, Balder B, Sjostrand M, Qvarfordt I, Linden A. Interleukin-17-producing T-helper cells and related cytokines in human airways exposed to endotoxin. *Eur Respir J*. 2010;36(5):1155-64.
5. Xia M, Viera-Hutchins L, Garcia-Lloret M, Noval Rivas M, Wise P, McGhee SA, Chatila ZK, Daher N, Sioutas C, Chatila TA. Vehicular exhaust particles promote allergic airway inflammation through an aryl hydrocarbon receptor-notch signaling cascade. *J Allergy Clin Immunol*. 2015;136(2):441-53.
6. Tischer C, Casas L, Wouters IM, Doekes G, Garcia-Esteban R, Gehring U, Hyvarinen A, Oldenwening M, Kerkhof M, Sunyer J, Standl M, Thiering E, Torrent M, Heinrich J, group Hs. Early exposure to bio-contaminants and asthma up to 10 years of age: results of the HITEA study. *Eur Respir J*. 2015;45(2):328-37.
7. Forno E, Celedon JC. Asthma and ethnic minorities: socioeconomic status and beyond. *Curr Opin Allergy Clin Immunol*. 2009;9(2):154-60.
8. Macartney S, Bishaw A, Fontenot K. Poverty Rates for Selected Detailed Race and Hispanic Groups by State and Place: 2007–2011 U.S. Census Bureau; 2013 Contract No.: Document Number|.
9. Thorne PS, Mendy A, Metwali N, Salo P, Co C, Jaramillo R, Rose KM, Zeldin DC. Endotoxin Exposure: Predictors and Prevalence of Associated Asthma Outcomes in the United States. *Am J Respir Crit Care Med*. 2015;192(11):1287-97.

TABLES

Table 1. Baseline characteristics of study participants obtained during initial study visit, overall and stratified by IL4R α -Q576R genotype. P-values represent univariate testing between genotype. Distribution of genotype differs by self-reported race, $p < 0.001$.

Characteristic	Overall	Q/Q genotype	Q/R genotype	R/R genotype	p-value
n	236	58	107	71	
Age in years (mean $\pm$ sd)	7.96 $\pm$ 1.91	8.00 $\pm$ 1.84	7.84 $\pm$ 2.01	8.11 $\pm$ 1.82	0.641
Male gender, n (%)	122 (51.7%)	27 (46.6%)	62 (57.9%)	33 (46.5%)	0.216
Self-reported race, n (%)					<0.001
Caucasian	12 (5.1%)	9 (15.5%)	3 (2.8%)	0 (0.0%)	
African-American	84 (35.6%)	11 (19.0%)	33 (30.8%)	40 (56.3%)	
Hispanic	82 (34.7%)	26 (44.8%)	44 (41.1%)	12 (16.9%)	
Other	42 (17.8%)	11 (19.0%)	19 (17.8%)	12 (16.9%)	
Mixed	16 (6.8%)	1 (1.7%)	8 (7.5%)	7 (9.9%)	
Annual income >\$25,000, n (%)	104 (44.1%)	30 (51.7%)	46 (43.0%)	28 (39.4%)	0.359
Family history of asthma, n (%)	187 (79.2%)	43 (74.1%)	88 (82.2%)	56 (78.9%)	0.470
Physician diagnosis of hayfever/ allergic rhinitis, n (%)	35 (14.9%)	7 (12.3%)	16 (15.0%)	12 (16.9%)	0.766
Physician diagnosis of eczema, n (%)	108 (45.8%)	19 (32.8%)	52 (48.6%)	37 (52.1%)	0.065
Allergic sensitization ^a (%)	159 (67.4%)	40 (69.0%)	77 (72.0%)	42 (59.2%)	0.195
Asthma severity ^b (%)					0.742
mild	20 (8.5%)	2 (3.4%)	11 (10.3%)	7 (9.9%)	
intermittent	47 (19.9%)	10 (17.2%)	21 (19.6%)	16 (22.5%)	
moderate	69 (29.2%)	18 (31.0%)	31 (29.0%)	20 (28.2%)	
severe	100 (42.4%)	28 (48.3%)	44 (41.1%)	28 (39.4%)	
Controller medication ^c use, n (%)	129 (54.7%)	30 (51.7%)	59 (55.1%)	40 (56.3%)	0.864
Use of rescue inhaler > 1x/week (%)	51 (21.6%)	11 (19.0%)	21 (19.6%)	19 (26.8%)	0.449
Asthma symptom days (mean $\pm$ sd) ^d	2.86 $\pm$ 4.09	2.60 $\pm$ 4.05	2.79 $\pm$ 4.05	3.18 $\pm$ 4.20	0.703

^a Allergic sensitization was defined as any positive skin prick test to 14 common aeroallergens or specific IgE level ≥ 0.35 kU/L on serologic testing

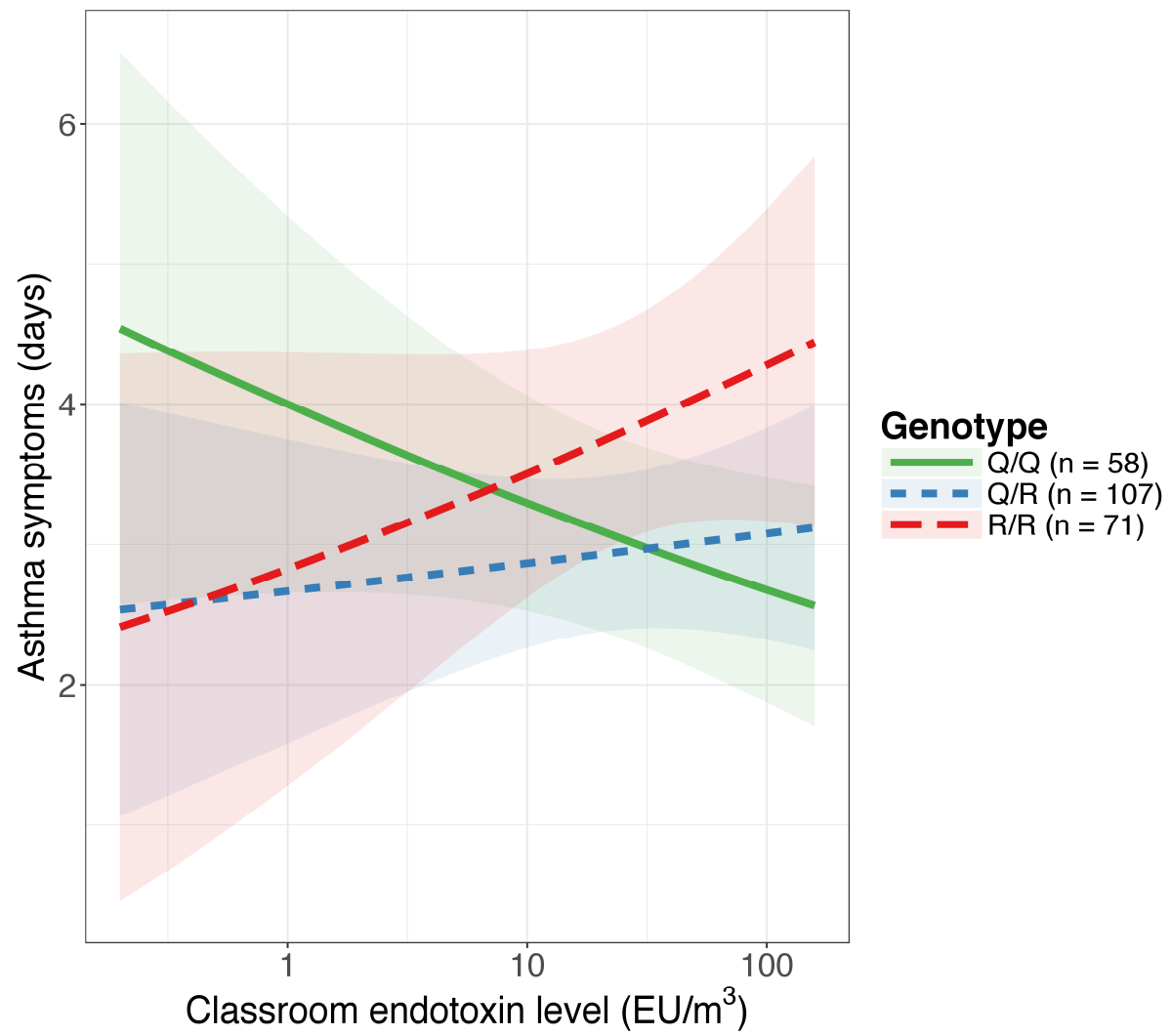
^b Asthma severity is graded based on recommendations from the National Asthma Education and Prevention Program, Third Expert Panel on the Diagnosis and Management of Asthma.

^c Controller medications are defined as use of an inhaled corticosteroid or leukotriene modifier, as ascertained by review of active prescriptions during baseline study visit.

^d Number of days with asthma symptoms noted by parent or caretaker in 14 days prior to initial clinic visit

FIGURE LEGENDS

Figure 1. Predicted asthma symptom days per two-week period associated with classroom endotoxin levels (log-transformed) stratified by IL4R α -Q576R genotype demonstrates a gene by environment (G $\times$ E) interaction. The overall interaction p-value = 0.09; pairwise interaction p-values for Q/R vs. Q/Q = 0.115, R/R vs. Q/Q = 0.049.



1 ONLINE REPOSITORY

3 Supplemental Methods

5 Detailed descriptions of the School Inner-city Asthma Study (SICAS) study has previously been
6 published^{1,2}, but will be briefly summarized here.

8 *Study design*

10 The School Inner-city Asthma Study (SICAS) is a single-center prospective cohort study of
11 children with persistent asthma attending inner-city elementary schools in a northeastern United
12 States city from 2008-2013. Children with persistent asthma attending these schools were
13 recruited based on established inclusion criterion³; 1) history of physician diagnosed asthma and
14 either current symptoms defined as cough, wheezing, shortness of breath, or whistling in the
15 chest in the past 12 months, daily controller medication use, or unscheduled medical visits for
16 asthma in the past year 2) attendance in grades kindergarten through 6th grade at a school where
17 permission for environmental sampling had been obtained. Exclusion criteria included any
18 significant pulmonary disease other than asthma. Written informed consent was obtained from
19 each participant's parent or legal guardian, and assent was obtained from each participant. The
20 protocol was approved by the Institutional Review Board (protocol number 07-11-0465) and the
21 participating school system.

23 *Study procedures*

25 Screening questionnaires were collected each spring in participating schools to identify eligible
26 asthmatics. Eligible subjects were invited to participate in a baseline comprehensive clinical
27 phenotyping evaluation during the summer, which included a detailed questionnaire and allergy
28 skin testing (MultiTest device, Lincoln Diagnostics, Decatur, IL) or specific IgE (ImmunoCAP,
29 Phadia AB, Uppsala, Sweden) if skin testing was contraindicated. Self-reported race was obtained
30 during this baseline clinic visit by asking the child's parent or taker a multiple-choice question as follows:
31 "How would you describe [CHILD]'s race, nationality, or ethnic background?" .

34 Home and classroom air and dust samples were subsequently collected twice during the
35 academic school year and linked to enrolled students and the temporally closest longitudinally
36 collected health outcomes. Follow-up phone surveys were administered by study staff
37 approximately 3, 6, 9, and 12 months after the initial visit.

39 School exposure assessment was performed in the fall and spring of the school year. One week
40 classroom airborne dust samples were collected using charged particle samplers (Quadra,
41 Sharper Image, California) based on a validated protocol^{4,5}. Collected dust was extracted in
42 buffered saline and the endotoxin content was measured using the Limulus amoebocyte lysate
43 assay (BioWhittaker Inc., Walkersville, MD).

45 The outcome of asthma symptom days is defined as follows, and is the same as that used in prior
46 urban pediatric asthma studies⁶⁻⁸. It is defined as the largest of the following variables in the 2
47 weeks prior to each follow-up survey; 1) daytime wheezing, chest tightness, or cough OR 2)

days on which child had to slow down or discontinue play activities due to wheezing, chest tightness, or cough OR 3) nights with wheezing, chest tightness, or cough leading to disturbed sleep.

The IL4R α -Q576R polymorphism is also referred to as the IL4R α -Q551R polymorphism depending on the amino acid numbering approach used. Genotyping was performed on blood or saliva samples collected during the baseline evaluation during the summer. Genotyping of the IL4R^{Q576} and IL4R^{R576} alleles was carried out using the amplification resistance mutation screen PCR method⁹ on DNA was extracted from either whole blood (Gentra Puregene Blood Kit; Qiagen) or saliva (prepIT L2P; DNA Genotek).

Statistical Analysis

The IL4R α -Q576R genotypes were modeled as a three-group categorical variable (Q/Q, Q/R, or R/R genotypes, with the Q/Q genotype as the reference group). We chose this approach because we did not want to assume a linear dose-response effect of the genotypes in our modeling approach. School endotoxin exposure was modelled as a log-transformed continuous variable given the skewed distribution. To test the hypothesis that the genotypes differed by self-reported race, Fisher's exact tests were performed. To test the hypothesis that a gene-environment interaction was present, a multiplicative term between classroom endotoxin levels (continuous) and genotype (3-level categorical variable) was included in binomial family generalized estimating equations with a logit link and an overdispersion parameter. These models included only observations during the school year, and adjusted for age, gender, self-reported race, allergic sensitization, baseline asthma severity, use of asthma controller medications, annual income, and season (using linear and quadratic terms for days since school start). All statistical analyses were performed in Stata version 13.1 (StataCorp). Two-sided p-values of <0.05 were considered statistically significant for main effects; p-values of <0.10 were considered statistically significant for interactions.

Supplemental Results

In univariate analyses adjusting for repeated measures of asthma symptom days in the same participant, the average number of asthma symptom days in a 14-day period for these children differed based on their IL4R α -Q576R polymorphism status, with average symptom days being 2.9 ± 4.0 , 3.0 ± 4.1 , and 3.6 ± 4.4 in children with the wild type, heterozygote, and homozygote mutant alleles, respectively, though these results did not reach statistical significance ($p = 0.33$). Similarly, in univariate analyses, the association between classroom endotoxin exposure and asthma symptom days did not reach statistical significance (OR= 1.11 [0.90,1.37], $p=0.31$).

Supplementary Table 1. Allele frequency by self-reported race for IL4R α -Q576R polymorphism.

Self-reported race	Q allele frequency	R allele frequency
White	0.875	0.125
Black	0.327	0.673
Hispanic	0.585	0.415
Other	0.488	0.512
Mixed	0.312	0.688

Supplementary Table 2. Predicted asthma symptom days per two-week period stratified by IL4R α -Q576R genotype and classroom endotoxin levels. There is a gene by environment (G $\times$ E) interaction. The overall interaction p-value = 0.09; pairwise interaction p-values for Q/R vs. Q/Q = 0.115, R/R vs. Q/Q = 0.049.

	Q/Q genotype	Q/R genotype	R/R genotype
10 th percentile endotoxin (3.06 EU/m ³)	3.6 [2.6 – 4.6] days	2.8 [1.9 – 3.6] days	3.1 [1.9 – 4.4] days
90th percentile endotoxin (153.11 EU/m ³)	2.6 [1.7 – 3.4] days	3.1 [2.3 – 4.0] days	4.4 [3.1 – 5.7] days

References cited:

1. Lai PS, Sheehan WJ, Gaffin JM, Petty CR, Coull BA, Gold DR, Phipatanakul W. School Endotoxin Exposure and Asthma Morbidity in Inner-city Children. *Chest*. 2015;148(5):1251-8.
2. Phipatanakul W, Bailey A, Hoffman EB, Sheehan WJ, Lane JP, Baxi S, Rao D, Permaul P, Gaffin JM, Rogers CA, Muilenberg ML, Gold DR. The school inner-city asthma study: design, methods, and lessons learned. *J Asthma*. 2011;48(10):1007-14.
3. Mitchell H, Senturia Y, Gergen P, Baker D, Joseph C, McNiff-Mortimer K, Wedner HJ, Crain E, Eggleston P, Evans R, 3rd, Kattan M, Kerckmar C, Leickly F, Malveaux F, Smartt E, Weiss K. Design and methods of the National Cooperative Inner-City Asthma Study. *Pediatric pulmonology*. 1997;24(4):237-52.
4. Platts-Mills J, Custis N, Kenney A, Tsay A, Chapman M, Feldman S, Platts-Mills T. The effects of cage design on airborne allergens and endotoxin in animal rooms: high-volume measurements with an ion-charging device. *Contemporary topics in laboratory animal science / American Association for Laboratory Animal Science*. 2005;44(2):12-6.
5. Custis NJ, Woodfolk JA, Vaughan JW, Platts-Mills TA. Quantitative measurement of airborne allergens from dust mites, dogs, and cats using an ion-charging device. *Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology*. 2003;33(7):986-91.
6. Rosenstreich DL, Eggleston P, Kattan M, Baker D, Slavin RG, Gergen P, Mitchell H, McNiff-Mortimer K, Lynn H, Ownby D, Malveaux F. The role of cockroach allergy and exposure to cockroach allergen in causing morbidity among inner-city children with asthma. *The New England journal of medicine*. 1997;336(19):1356-63.
7. Morgan WJ, Crain EF, Gruchalla RS, O'Connor GT, Kattan M, Evans R, 3rd, Stout J, Malindzak G, Smartt E, Plaut M, Walter M, Vaughn B, Mitchell H, Inner-City Asthma Study G. Results of a home-based environmental intervention among urban children with asthma. *The New England journal of medicine*. 2004;351(11):1068-80.
8. Busse WW, Morgan WJ, Gergen PJ, Mitchell HE, Gern JE, Liu AH, Gruchalla RS, Kattan M, Teach SJ, Pongracic JA, Chmiel JF, Steinbach SF, Calatroni A, Togias A, Thompson KM, Szeffler SJ, Sorkness CA. Randomized trial of omalizumab (anti-IgE) for asthma in inner-city children. *The New England journal of medicine*. 2011;364(11):1005-15.
9. Massoud AH, Charbonnier LM, Lopez D, Pellegrini M, Phipatanakul W, Chatila TA. An asthma-associated IL4R variant exacerbates airway inflammation by promoting conversion of regulatory T cells to TH17-like cells. *Nat Med*. 2016;22(9):1013-22.