Protection from asthma in a high-risk birth cohort by attenuated P2X<sub>7</sub> function

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Background: Viral illnesses are important factors in both asthma inception and exacerbations, and allergic sensitization in early life further enhances asthma risk through unclear mechanisms. Cellular damage caused by infection or allergen inhalation increases ATP levels in the airways with subsequent purinergic receptor activation. The purinergic receptor P2X<sub>7</sub> can enhance airway leukocyte recruitment to the airways, and P2X<sub>7</sub> knockout mice display a reduced asthma-like phenotype. Objective: Based on the P2X<sub>7</sub> knockout mouse, we hypothesized that children with low P2X<sub>7</sub> function would have decreased rates of asthma.

Methods: We used a functional assay to determine P2X<sub>7</sub> pore-producing capacity in whole-blood samples in a birth cohort at high risk for asthma development. The P2X<sub>7</sub> assay was validated with known loss-of-function alleles in human subjects. P2X<sub>7</sub> pore status categorization was used to assess asthma and allergy status in the cohort.

Results: Attenuated P2X<sub>7</sub> function was associated with lower asthma rates at ages 6 and 8 years, and the greatest effects were observed in boys. Children with asthma at age 11 years who had low P2X<sub>7</sub> capacity had less severe disease in the previous year. Attenuated P2X<sub>7</sub> function was also associated with sensitization to fewer Aeroallergens.

Conclusion: P2X<sub>7</sub> functional capacity is associated with asthma risk or disease severity, and these relationships appear to be age related. (J Allergy Clin Immunol 2012;130:496-502.)

Key words: Asthma, allergy, children, P2X<sub>7</sub>, ATP

Sensitization to Aeroallergens and the Occurrence of Virus-associated Wheezing Illnesses Are Early Childhood Events Known to Increase the Risk of Asthma, and the Occurrence of Either Is Thought to Be a Balance Between Environmental and Host Factors.1,2 Our Group Previously Reported a Significantly Increased Risk of Asthma at Age 6 Years with Acute Wheezing Illnesses in the First 3 Years of Life Associated with Human Rhinovirus (HRV),3 and Aeroallergen Sensitization Might Contribute to the Risk of More Severe Virus-induced Wheezing Illnesses and Asthma.4,6 The Risk of HRV-induced Wheeze Might Also Depend on Factors Related to the Virus,7,9 and Susceptible Subjects Can Be Identified Based on Attenuated Antiviral Defense Mechanisms Leading to Compromised Type I and III Interferon Production.10-12 Unfortunately, Less Is Known about the Control of Allergic Sensitization and the Diverse Molecular Patterns and Innate Immune Receptors Comprising Recognition of Aeroallergens.13-16 Additionally, the Transition From Innate to Adaptive Immune Responses Is Thought to Be Pivotal in the Development of Sensitization.17-19 A Recent Example Is the Observation That Chronic Activation of Dendritic Cells (DCs) Enhances the Development of Poly sensitization to New Aeroallergens.20 Although These Findings Have Provided New Insights, Determining Additional Characteristics of Aeroallergen-host Interactions Will Further Identify Potential Interventions Important in Asthmatic Patients.

In this regard a growing body of evidence supports the function of nucleotides and nucleotide receptors in the regulation of innate to adaptive responses.15,21,22 Injury and inflammation in the lung lead to cell damage and subsequent release of intracellular danger signals in the airways, including ATP,23-25 a natural ligand for a family of purinergic receptors.26 Granulocytic cell influx to the airways after allergen challenge is linked to ATP levels and is blunted when ATP is hydrolyzed or purinergic receptor antagonists are administered.25,26 Specifically, an absence of P2X<sub>7</sub> leads to a lack of proinflammatory cytokine IL-1β release28 and prevents contact dermatitis in a murine model.29 A sensitization and exposure model of allergic asthma in P2X<sub>7</sub> knockout mice showed decreased airway reactivity and fewer immune cells.
recruited to the lung after challenge.30 The immunologic amplification loop involving extracellular ATP and P2X7 has been implicated in a growing number of diseases in which the resulting pathology is determined by the site at which ATP is released, including at neuroreceptors and in the liver, vasculature, and the lung.29-33

Because P2X7 contributes to responses from both allergens and pathogens, we sought to assess the association between P2X7 function and the development of asthma in a birth cohort at high risk for asthma and allergy.34 The gene encoding the P2X7 receptor (P2RX7) is polymorphic, with nonsynonymous single nucleotide polymorphisms resulting in functional alterations.35 These functional differences allow us to use a flow cytometric assay to assess whether a subject’s P2RX7 genotype confers normal or loss-of-function (LOF) potential for cell membrane pore formation.36,37 Based on the P2RX7 knockout mouse,30 we hypothesized that low P2X7 pore function would confer protection against asthma. We demonstrate that low functioning P2X7, as measured in peripheral blood monocytes, is associated with reduced risk of childhood asthma and allergic sensitization.

METHODS

Study subjects
The participants were part of the Childhood Origins of Asthma (COAST) study, a previously described longitudinal study of a birth cohort that enrolled 289 children at high risk of asthma.34 All children had at least 1 parent with a history of physician-diagnosed asthma, respiratory allergies, or both. All experiments were performed with approval of the Institutional Review Board and Human Subjects Committee at the University of Wisconsin–Madison; consent was obtained from the children, and informed consent was obtained from the children’s parents.

Current asthma was defined at ages 6, 8, and 11 years, as described previously,3 and asthma severity was assessed at age 11 years. Briefly, current asthma was diagnosed on the basis of the documented presence of 1 or more of the following in the previous year: (1) a physician’s diagnosis of asthma; (2) use of albuterol for coughing or wheezing episodes (prescribed by a physician); (3) use of a daily controller medication; (4) step-up plan including use of albuterol or short-term use of inhaled corticosteroids during illnesses; and (5) use of prednisone for asthma exacerbation. Asthma severity was assessed at the 11-year visit based on the National Asthma Education and Prevention Program’s Expert Panel Report 3 criteria. For children using long-term controller medications, severity was classified by the level of treatment required for control of asthma, whereas children not receiving controller therapy were classified based on symptoms.38

Wheezing respiratory tract illnesses in the first 3 years of life were previously defined by 1 or more of the following: (1) physician-diagnosed wheezing at an office visit; (2) an illness for which a child was prescribed short- or long-acting β-agonists, controller medications, or both; and (3) an illness given the following diagnoses: bronchiolitis, wheezing illness, reactive airway disease, asthma, and/or asthma exacerbation.3

P2X7 pore assay
Peripheral blood samples in citrate tubes were obtained from COAST children during annual study visits at ages 10 and 11 years for whole-blood pore assays to assess P2X7 function.39 Briefly, 500 μL of room temperature blood was rinsed twice with HEPES-buffered saline (HBS; 130 mmol/L NaCl, 5 mmol/L KCl, 20 mmol/L HEPES, 0.1% BSA, and 10 mmol/L glucose [pH 7.4]) and incubated with CD14 conjugated to phycoerythrin (CD14-PE; BD Biosciences, San Diego, Calif) in HBS for 20 minutes. Samples were rinsed twice with potassium glutamate buffer (130 mmol/L potassium glutamate, 5 mmol/L KCl, 20 mmol/L HEPES, 0.1% BSA, and 10 mmol/L glucose [pH 7.4]) and incubated with 250 μmol/L 2’(3’)-(O-4-benzoylbenzoyl) ATP (BzATP; Sigma, St Louis, Mo) and 1 μmol/L YO-PRO-1 (Molecular Probes, Eugene, Ore) in potassium glutamate buffer for 20 minutes before addition of magnesium chloride and HBS washing. Viable CD14+ cells identified by using propidium iodide exclusion were examined for YO-PRO-1 median fluorescence intensity (MFI) by using bead-adjusted (BD Calibrite Beads, BD Biosciences) and calibrated (RFP-30-5A; Spherotech, Lake Forest, Ill) flow cytometry on a FACSCalibur (BD Biosciences). Archived DNA from COAST participants was genotyped in the laboratory of Dr Carole Ober (University of Chicago, Chicago, Ill). An adult population previously genotyped for P2RX7 and with P2X7 pore function measurements was also used for comparison.37 By using our previous methods,39,5 functionally validated P2RX7 LOF alleles were used to genomically validate the threshold of whole-blood P2X7 pore activity discriminating normal and attenuated function in both children and adults. A receiver operating characteristic curve was used to instruct the threshold between low and normal P2X7 pore activity by maximizing sensitivity and specificity in identification of P2RX7 LOF alleles.

Allergen-specific IgE measurement
Allergen-specific IgE levels were measured in plasma by using an automated fluoroenzyme immunoassay (Unicap 100; Pharmacia Diagnostics AB, Uppsala, Sweden). At ages 1, 3, 6, and 9 years, IgE levels were measured for 2 species of dust mites (Dermatophagoides farinae and Dermatophagoides pteronyssinus), Alternaria alternata, cat dander, and dog. At ages 6 and 9 years, IgE levels were additionally measured for ragweed, birch, timothy grass, and cockroach.40 Test results were considered positive for values of 0.35 kU/L or greater.

Statistical analysis
The relationships between children’s P2X7 pore function MFI values measured on different days and obtained at different ages were examined by using the Pearson correlation coefficient. Logistic regression was used to examine the relationships of asthma and viral wheezing outcomes to pore status. Multivariate logistic regression models of asthma included pore status and either sex or HRV-induced wheeze and the interaction term as covariates. The Pearson correlation coefficient. Logistic regression was used to examine the relationships of asthma and viral wheezing outcomes to pore status. Multivariate logistic regression models of asthma included pore status and either sex or HRV-induced wheeze and the interaction term as covariates. The χ2 test for association was used to compare aeroallergen sensitization rates by pore status and early-life demographic and risk factors by pore status. Birth weight for association was used to compare the association between asthma severity and viral wheezing outcomes to pore status. Multivariate logistic regression models of asthma included pore status and either sex or HRV-induced wheeze and the interaction term as covariates. The χ2 test for association was used to compare aeroallergen sensitization rates by pore status and early-life demographic and risk factors by pore status. Birth weight for association was used to compare the association between asthma severity and viral wheezing outcomes to pore status. Multivariate logistic regression models of asthma included pore status and either sex or HRV-induced wheeze and the interaction term as covariates. The χ2 test for association was used to compare aeroallergen sensitization rates by pore status and early-life demographic and risk factors by pore status. Birth weight for association was used to compare the association between asthma severity and viral wheezing outcomes to pore status. Multivariate logistic regression models of asthma included pore status and either sex or HRV-induced wheeze and the interaction term as covariates. The χ2 test for association was used to compare aeroallergen sensitization rates by pore status and early-life demographic and risk factors by pore status. Birth weight for association was used to compare the association between asthma severity and viral wheezing outcomes to pore status. Multivariate logistic regression models of asthma included pore status and either sex or HRV-induced wheeze and the interaction term as covariates. The χ2 test for association was used to compare aeroallergen sensitization rates by pore status and early-life demographic and risk factors by pore status. Birth weight for association was used to compare the association between asthma severity and viral wheezing outcomes to pore status.

RESULTS

P2X7 pore assay characteristics
At least 1 P2X7 pore assay was performed on 172 children in COAST during annual visits at ages 10 and 11 years. Assay results were similar to those previously performed on adults, with an approximately square root normalized distribution (Fig 1, A). To validate the reproducibility of our standard methods, a subset of 48 samples had pore assays performed on more than 1 day after
phlebotomy, with an average daily coefficient of variation of 7% between the first and second day (Pearson \( r = 0.97, P < .001 \); Fig 1, B). Additionally, a subset of 71 children had pore assays performed at both the 10- and 11-year study visits, and the year-to-year reproducibility of the assay was also highly correlated (Pearson \( r = 0.91, P < .001 \); Fig 1, C). Overall, these results confirm the high reproducibility of our pore assay and independence from potential technical confounding factors.

Because the COAST P2X7 pore assays were consistent with previous adult assays, we combined both for receiver operating characteristic analysis using 5 validated P2RX7 LOF alleles to determine a threshold between subjects with low and normal P2X7 function (Fig 1, D). From this analysis, a threshold MFI of 382 was identified and used to categorize all subjects with P2X7 pore assays with either low or normal P2X7 pore status, as indicated by the shading in Fig 1, A. The resulting performance properties of the assay in identifying LOF alleles for P2RX7 are shown in Fig 1, D (area under the curve = 0.90), which is indicated as the labeled point in the upper left corner, maximizing both sensitivity and specificity.

![FIG 1. P2X7 pore assay characteristics. A, P2X7 pore assay distributions for COAST (n = 172) and adult (n = 156) populations are shown. Lighter shading indicates low P2X7 function. B and C, P2X7 pore assays are shown for the same sample at different days after phlebotomy (\( r = 0.97, P < .001 \); Fig 1, B) and at different subject ages (\( r = 0.91, P < .001 \); Fig 1, C). D, A receiver operating characteristic curve (area under the curve = 0.90) is shown with characteristics for identifying P2RX7 LOF alleles based on the optimized threshold MFI of 382, which is indicated as the labeled point in the upper left corner, maximizing both sensitivity and specificity.](image)

<table>
<thead>
<tr>
<th>TABLE I. P2X7 function is independent of asthma risk factors</th>
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<tbody>
<tr>
<td>Birth and year 1 risk factors</td>
</tr>
<tr>
<td>-------------------------------------------------------------</td>
</tr>
<tr>
<td>Maternal asthma ever</td>
</tr>
<tr>
<td>Paternal asthma ever</td>
</tr>
<tr>
<td>Smoke exposure in year 1</td>
</tr>
<tr>
<td>Day care attendance in year 1</td>
</tr>
<tr>
<td>Exclusive breast-feeding during first 6 mo</td>
</tr>
<tr>
<td>Dog in home at birth</td>
</tr>
<tr>
<td>Cat in home at birth</td>
</tr>
<tr>
<td>Older siblings</td>
</tr>
<tr>
<td>Active atopic dermatitis in year 1</td>
</tr>
<tr>
<td>Birth month</td>
</tr>
<tr>
<td>Birth weight ± SD (oz)</td>
</tr>
<tr>
<td>Male sex</td>
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</tbody>
</table>

Subjects’ characteristics were stratified by P2X7 function.

P2X7 function, asthma inception, and disease severity

To determine the association between P2X7 function and childhood asthma, we stratified the COAST cohort using P2X7 pore status and determined the rates of asthma at ages 6, 8, and 11 years. Low P2X7 pore status was associated with a decreased rate of asthma (Fig 2, A) at ages 6 (odds ratio [OR], 0.34; 95% CI, 0.15-0.79; \( P = .01 \)) and 8 (OR, 0.42; 95% CI, 0.20-0.88; \( P = .02 \)) years, but a significant association was not observed at

P2X7 pore status is independent of many demographic factors

To determine whether P2X7 status was biased by risk factors at birth or in the first year of life, we examined the distribution of pore status across a number of risk factors for asthma. P2X7 pore status was independent of birth and early-life characteristics (Table I).
age 11 years (OR, 0.62; 95% CI, 0.29-1.31; P = .21). To investigate whether there were any phenotypic effects in the children with asthma at age 11 years, we also stratified the severity of asthma using P2X7 function. Asthmatic children with low P2X7 pore function at age 11 years had evidence of less severe asthma compared with asthmatic children with normal P2X7 pore function (P = .03; Fig 2, B). However, when examined at age 6 years, P2X7 pore function was not associated with asthma severity (P = .29). Children with low pore function and asthma at age 11 years were also less likely to have used a step-up short-term plan, which is used for temporary loss of acceptable control with respiratory tract illnesses,41 in the previous year (OR, 0.26; 95% CI, 0.07-0.90; P < .05). However, when examined at age 6 years, P2X7 pore function was not associated with asthma severity (P = .29).

P2X7 function is associated with early-life wheezing with HRV

Because of P2X7’s role in infections and airway reactivity30,42 and our previous observation that wheezing illnesses associated with HRV in the first 3 years of life correspond to an increased rate of asthma,3 we assessed the rates of wheezing in early life with or without virus detected based on P2X7 function groups. Low P2X7 pore status was not associated with preschool wheezing in general but was associated with decreased wheezing associated with HRV infections in the first 3 years of life (Table II).

Decreased asthma risk associated with attenuated P2X7 function is varied by a history of HRV-induced wheezing and sex

To test whether reduced asthma risk in subjects with low P2X7 function was only due to the association with decreased early-life HRV wheezing, we modeled the interaction of P2X7 status and HRV-induced wheezing on asthma diagnosis by using logistic regression. The greatest risk for asthma was present in children who had the combination of normal P2X7 function and a history of HRV-induced wheezing in the first 3 years of life (Fig 3, A) and P2X7 status and sex (Fig 3, B) displayed an interactive effect on asthma risk. *P < .05 for logistic regression model interaction terms. F, Female; HRV Whz, wheezing with HRV during first 3 years of life; Lo, low P2X7 function; M, male; NL, normal P2X7 function.

![Figure 2](image1.png)

**FIG 2.** Low P2X7 pore function is protective against asthma development. A, The rates of asthma at ages 6, 8, and 11 years are shown for low and normal P2X7 status. B, Asthma severity at age 11 years is shown stratified by P2X7 pore status. Inter, Intermittent; Mod, moderate. *P < .05.

![Figure 3](image2.png)

**FIG 3.** Interactions of P2X7 with HRV-induced wheezing and sex. A and B, Both P2X7 status and HRV-induced wheezing in the first 3 years of life (Fig 3, A) and P2X7 status and sex (Fig 3, B) displayed an interactive effect on asthma risk. *P < .05 for logistic regression model interaction terms. F, Female; HRV Whz, wheezing with HRV during first 3 years of life; Lo, low P2X7 function; M, male; NL, normal P2X7 function.

![Table II](image3.png)

**TABLE II.** P2X7 and early-life wheezing

<table>
<thead>
<tr>
<th>Wheezing illnesses in first 3 y</th>
<th>Low (n = 48)</th>
<th>Normal (n = 124)</th>
<th>OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any cause</td>
<td>44%</td>
<td>52%</td>
<td>0.71 (0.36-1.38)</td>
<td>.31</td>
</tr>
<tr>
<td>RSV detected</td>
<td>19%</td>
<td>31%</td>
<td>0.50 (0.22-1.14)</td>
<td>.10</td>
</tr>
<tr>
<td>HRV detected</td>
<td>19%</td>
<td>40%</td>
<td>0.35 (0.16-0.79)</td>
<td>.01</td>
</tr>
</tbody>
</table>

Wheezing illnesses in the first 3 years of life were compared between low and normal P2X7 pore function groups. RSV, Respiratory syncytial virus.
The model no longer remained significant across both years measured only at ages 6 and 9 years, a similar trend was observed, in children with low P2X7 function were sensitized to fewer aeroallergens at age 6 years (Fig 4, A). Because increased activation of DCs is reported to increase rates of polysensitization,20 we also examined the rates of sensitization to aeroallergens as the average number of positive sensitizations per child. When 5 common aeroallergens were modeled by using mixed-effects quasi-Poisson regression, children with low P2X7 function were sensitized to fewer aeroallergens across ages 1, 3, 6, and 9 years (mean fold change, 0.45; 95% CI, 0.22-0.91; P = .03; Fig 4, B). At individual ages, children with low P2X7 function were sensitized to significantly fewer allergens at age 6 years (P = .02), and children with low P2X7 function trended to be sensitized to fewer allergens at ages 3 (P = .09) and 9 (P = .07) years. When including additional aeroallergens measured only at ages 6 and 9 years, a similar trend was observed, but the model no longer remained significant across both years (P = .14).

**DISCUSSION**

This study adds to a growing body of research revolving around the role of nucleotides in airway disease. Similar to previous work in adults, we demonstrate good performance of a whole-blood P2X7 function assay as a method to detect P2RX7 LOF alleles (Fig 1). By using this robust assay, we have demonstrated that a lack of P2X7 pore activity in high-risk children is associated with a reduced risk of asthma (Fig 2), as well as sensitization to fewer aeroallergens (Fig 4). However, the mechanisms underlying these observations are not clear. Discerning the role of P2X7 activation by extracellular ATP in concert with secondary signals, including allergen exposure, viral infections, or both, might help determine how P2X7 activity could modulate the risk of chronic conditions, such as asthma.

Previous studies indicate that the amount of extracellular ATP might be related to airway disease severity.25 Rather than directly measuring ATP levels in the airway after injurious events, our study has the strength to study the potential for differential host responses to natural in vivo extracellular ATP fluctuations. Our results (Fig 1, D) recapitulate that considerably more contributes to P2X7 pore function than validated P2RX7 LOF alleles and illustrate the power of our functional approach to evaluate potential gene-environment interactions. The COAST population has already demonstrated gene-environment interactions, including between IFNG and sex,46 which might be important to in vivo P2X7 function because IFN-γ reportedly regulates P2X7.45 Although our current results are from prepubertal children, they display a varied risk of asthma by P2X7 status based on sex (Fig 3, B). Whether the dynamics of this relationship change during and after puberty will be of great interest.

Our current results are in general agreement with findings from P2X7 knockout mice, wherein low P2X7 function is protective from asthma-like symptoms.30 These P2X7 knockout mice demonstrate decreased cell influx into the lung after allergen or smoke challenge,30,46 and we have previously shown decreased neutrophil infiltration in the nose during an acute cold in adults with low P2X7 function.47 Although our current study might have been strengthened if P2X7 pore assays could have been performed in early life before the earliest asthma evaluations, the high reproducibility and genetic basis of our results (Fig 1) indicate that assays should be similar at any age and mitigate these potential concerns.

Although low P2X7 pore status protection against asthma in the current COAST cohort is consistent over multiple ages, these results seem counter to the inverse relationship between P2X7 function and exacerbation risks in adults with a natural cold.47 Differences in study populations and in the pathogenesis of asthma inception compared with exacerbations might help reconcile these findings. There are significant differences in study populations: the COAST population is comprised of high-risk children followed prospectively from birth, whereas the previous study enrolled symptomatic asthmatic adults during the peak cold season. In the children asthma was more common in boys, whereas in adults asthma was predominately observed in women. It is possible that the overall lack of association at age 11 years between asthma and P2X7 status might continue to change throughout puberty into adulthood and reflect the exacerbation risks observed in adults. Specifically, it is intriguing to note that a small percentage of children had both low P2X7 status and a history of HRV-induced wheezing and that this group demonstrated the largest shift in rates of current asthma at different ages. Whether modification of P2X7 function from nucleotide activation is sufficient to alter asthma outcomes in human subjects has yet to be measured.

How does P2X7 influence asthma risk? Although P2X7 is present in airway epithelial cells, the receptor is more highly

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**FIG 4.** Aeroallergen sensitization status. A, The prevalence of children with positive sensitization to any aeroallergen measured is stratified by P2X7 function. The average number of allergens to which each subject was sensitized was stratified by P2X7 function. For both panels, aeroallergens measured during all 4 ages are shown on the left, and inclusion of additional aeroallergens measured at ages 6 and 9 years is shown on the right. Error bars are the SEMs. *P < .05. †P < .1.

**Allergic polysensitization and P2X7 status**

Effects of P2X7 function on allergic sensitization rates have not previously been tested. In COAST, children with low P2X7 function were less likely to be sensitized to common aeroallergens at age 3 years (P = .04), with a similar trend at age 9 years (P = .07; Fig 4, A). Because increased activation of DCs is reported to increase rates of polysensitization,20 we also examined the rates of sensitization to aeroallergens as the average number of positive sensitizations per child. When 5 common aeroallergens were modeled by using mixed-effects quasi-Poisson regression, children with low P2X7 function were sensitized to fewer aeroallergens across ages 1, 3, 6, and 9 years (mean fold change, 0.45; 95% CI, 0.22-0.91; P = .03; Fig 4, B). At individual ages, children with low P2X7 function were sensitized to significantly fewer allergens at age 6 years (P = .02), and children with low P2X7 function trended to be sensitized to fewer allergens at ages 3 (P = .09) and 9 (P = .07) years. When including additional aeroallergens measured only at ages 6 and 9 years, a similar trend was observed, but the model no longer remained significant across both years (P = .14).
expressed and active in immune cells, including DCs. Both nucleotides and nucleotide receptors, including P2X7, affect DC function and loss of P2X7 function, specifically from LOF alleles detected by using our pore assay, leads to a decrease in DC pore activity, as well as other P2X7-dependent functional responses. T-cell maturation, including regulatory T and Tef17 cell phenotypes, is modified by nucleotide activity on T cells and DCs, either directly or by engaging pathways associated with P2X7, including the NLRP3 inflammasome or pannexin-1, and this suggests that functional P2X7 activation might lead to a decrease in regulatory T-cell populations. A DC-focused role of P2X7 is supportive of an amplified response to infections or allergens when coningled with danger signals acting as adjuvants. Our study demonstrates a potential role for monitoring host responsiveness to immunomodulatory danger signals.

P2X7 sits at a balance point in the immune system in response to allergic and infectious events. It is not clear whether a single episode of P2X7 activation is sufficient to increase the risk of asthma or whether frequent stimulation is required. Moreover, P2X7 function might not always be beneficial or harmful in the immune response; the role of P2X7 might be different when comparing disease inception with active chronic conditions with superimposed acute events, such as exacerbations. As examples, influenza virus activation of the inflammasome has been linked to P2X7 function, whereas another report suggests P2X7 activation might decrease susceptibility to diseases, including asthma. We thank all study participants and past and present coordinators of COAST. We also thank Dr. Carole Ober, PhD, University of Chicago, for assistance with sample genotyping.

Key messages
- P2X7 functional capacity is easily assessed in children.
- Low P2X7 function might decrease susceptibility to diseases, including asthma.

REFERENCES


