Paternal History of Asthma and Airway Responsiveness in Children with Asthma

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Rationale: Little is known regarding the relationship between parental history of asthma and subsequent airway hyperresponsiveness (AHR) in children with asthma. **Objectives:** We evaluated this relationship in 1,041 children with asthma participating in a randomized trial of antiinflammatory medications (the Childhood Asthma Management Program [CAMP]). **Methods:** Methacholine challenge testing was performed before treatment randomization and once per year over an average of 4.5 years postrandomization. Cross-sectional and longitudinal repeated measures analyses were performed to model the relationship between PC₂₀ (the methacholine concentration causing a 20% fall in FEV₁) with maternal, paternal, and joint parental histories of asthma. Models were adjusted for potential confounders. **Measurements and Main Results:** At baseline, AHR was strongly associated with a paternal history of asthma. Children with a paternal history of asthma demonstrated significantly greater AHR than those without such history (median log_ePC₂₀, 0.84 vs. 1.13; $p = 0.006$). Although maternal history of asthma was not associated with AHR, children with two parents with asthma had greater AHR than those with no parents with asthma (median log_ePC₂₀, 0.52 vs. 1.17; $p = 0.0008$). Longitudinal multivariate analysis of the relation between paternal history of asthma and AHR using repeated PC₂₀ measurements over 44 months postrandomization confirmed a significant association between paternal history of asthma and AHR among children in CAMP. **Conclusions:** Our findings suggest that the genetic contribution of the father is associated with AHR, an important determinant of disease severity among children with asthma.

Keywords: airway responsiveness; asthma; genetics; longitudinal analysis; parent of origin

Airway hyperresponsiveness (AHR), the exaggerated constrictor response of the airways to a variety of stimuli, is a cardinal feature and a defining characteristic of asthma (1). Among indi-

viduals with asthma, AHR is directly correlated with pulmonary symptoms and disease severity (2) and is an important determinant of long-term outcome, not only with respect to asthma symptoms (3) but also to airway growth and maturation (4) and lung function decline (5). AHR improves after long-term inhaled corticosteroid use, resulting in reduced frequencies of asthma exacerbations and hospital visits (6). Elucidating the environmental and genetic determinants of this marker of asthma severity is of critical importance, yet few studies have formally evaluated the natural history of airways responsiveness among children with asthma.

General population studies of twins and others of nuclear families with asthma have demonstrated that AHR is a heritable trait, with an estimated heritability of 30 to 66% (7, 8). In cross-sectional assessments, others have observed that parental history of asthma is a determinant of AHR in the child (9–11). In contrast, little is known regarding the impact of parental history of asthma and allergy on the natural history of airway responsiveness among children with established asthma. We examined this relationship in the Childhood Asthma Management Program (CAMP), in which annual measurements of airway responsiveness over an average of 4.5 years were available for 1,041 children who participated in a 5-year clinical trial.

METHODS

Details of the design and methods of the CAMP trial and the results of the initial clinical trial are published elsewhere (6, 12). CAMP is a multicenter, randomized, double-masked clinical trial designed to compare the long-term safety and effectiveness of inhaled treatments for mild to moderate childhood asthma. CAMP enrolled 1,041 children ages 5 to 12 years with mild to moderate asthma over a 22-month period. Children had to have a history of asthma, as evidenced by one or more of the following findings, for at least 6 months in the year before enrollment: (1) asthma symptoms at least twice a week, (2) inhaled bronchodilator use at least twice a week, and (3) use of daily asthma medication. All study participants had to have AHR to methacholine (defined as a provocative concentration of methacholine causing a 20% reduction in FEV₁ [PC₂₀] no greater than 12.5 mg/ml). Children with evidence of severe asthma or other clinically significant conditions were excluded (6, 12). After baseline evaluations, participants were randomized to one of three inhaled treatment arms: (1) budesonide (311 children), (2) nedocromil sodium (312 children), and (3) placebo (418 children). Follow-up visits occurred 2 and 4 months after randomization and at 4-month intervals thereafter. Questionnaire data, including family history data, were collected by interview of parents/guardians/patients by the research coordinator. Spirometry was performed twice yearly, and methacholine challenge was performed annually (at 8, 20, 32, 44, and 56 months after randomization). Details regarding questionnaire data and methodology for spirometry and methacholine challenge testing are available in the online supplement.

The distribution of PC₂₀ at each visit was skewed, with a long right tail. PC₂₀ was therefore log-transformed for all regression analyses. There were four instances at baseline and 11 during follow-up where study participants were responsive to diluent (i.e., 0.000 for their PC₂₀). In these instances, PC₂₀ was imputed with a value of 0.023 mg/ml.

Linear regression using the method of least squares (13) was used

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to test the association between parental history of asthma or atopy and baseline PC₂₀ before and after adjustment for potential confounders. Logistic regression (14) was used to obtain unadjusted and adjusted effect estimates of parental history of asthma and atopy on the risk of having a PC₂₀ greater than 12.5 mg/ml at the 44-month visit. Variables considered for inclusion in all multivariable models are listed in the online supplement.

Longitudinal data analysis was performed to distinguish interindividual changes in PC₂₀ from within-subject change. We developed random-effects models using SAS PROC MIXED (SAS Institute, Cary, NC) (15, 16). We related log-transformed PC₂₀ to the aforementioned effects and accounted for associated time observations within a patient; components of variability were a random intercept supplemented with serial correlation. Details of this model are available in the online supplement. Analyses were performed with SAS version 8.2 (SAS Institute) (17). Each patient's parent or guardian signed a consent statement. The human research committees of several participating clinical centers also required study participants sign an approved assent statement.

RESULTS

A total of 1,041 children with asthma who were enrolled in the CAMP clinical trial underwent baseline methacholine challenge tests. Baseline test results from three individuals were deemed unreliable. Over the subsequent 4 years of evaluation, methacholine PC₂₀ measurements were obtained for 92, 90, 85, and 82% of the cohort at 8, 20, 32, and 44 months after randomization, respectively. Although baseline characteristics were generally similar between children with and without methacholine PC₂₀ measurements at 44 months, children who were missing measurements at 44 months were more likely to have been recruited from three clinical centers (Albuquerque, Boston, and Seattle), to come from families with lower household income, and to have mothers with a history of either asthma or smoking during pregnancy. Prerandomization FEV₁/FVC ratio, total IgE level, and baseline median log_e methacholine PC₂₀ (0.077 vs. 0.083) were similar between groups (Wilcoxon rank sum *p* values > 0.30 in all instances).

The distribution of baseline characteristics for the 1,041 children and their relationship to prerandomization log_ePC₂₀ are displayed in Table 1. As described previously (2), baseline log_ePC₂₀ differed by clinical center and was strongly correlated with family history of asthma. Baseline log_ePC₂₀ was also correlated with a personal history of hay fever and asthma severity. There was no association between baseline log_ePC₂₀ and age of child at randomization, sex, ethnicity, annual household income, highest level of education, or parental tobacco use. Compared with children without a parental history of asthma, children with a parental history of asthma on average had an earlier onset of asthma symptoms (2.82 vs. 3.27 years, *p* = 0.004), were more likely to have a history of allergic rhinitis (60.1 vs. 48.9%, *p* = 0.0005), and were more likely to have moderate (vs. mild) asthma at baseline (50.1 vs. 37.1%, *p* = 0.0001). There were no significant differences in the prevalence of either paternal (*p* = 0.15) or maternal (*p* = 0.93) history of asthma by assigned treatment group (budesonide vs. nedocromil vs. placebo).

The relationships between parental history of asthma or atopy and baseline log_e methacholine PC₂₀ are presented in Table 2. After adjustment for potential confounders, paternal history of asthma was strongly associated with baseline methacholine log_ePC₂₀. In contrast, baseline methacholine log_ePC₂₀ did not differ significantly by maternal history of asthma. Children with both maternal and paternal histories of asthma had a significantly greater degree of airway responsiveness than children with no history of asthma in either parent. The relationships between paternal history of asthma and AHR remained significant after adjustment for baseline FEV₁, although the strength of the relationship was weakened. Additional adjustment for baseline level

of airway obstruction (FEV₁/FVC ratio) resulted in a further weakening of the relationship between paternal history of asthma and airway responsiveness in the child, likely because of a strong association between paternal history of asthma and a lower baseline FEV₁/FVC ratio (*p* = 0.003). Subsequent longitudinal modeling suggests that the relationship between parental history of asthma and FEV₁/FVC is less consistent than the longitudinal relationship of parental history of asthma with AHR (*see below*). There was no significant association between baseline methacholine log_ePC₂₀ and either maternal or paternal history of atopy.

We assessed the relationship between parental history of asthma or atopy and methacholine log_ePC₂₀ over the course of the CAMP clinical trial (Figure 1). On the basis of population-average profiles, airway responsiveness to methacholine decreased significantly over the course of the clinical trial: the mean log_ePC₂₀ (95% confidence interval [CI]) increased from 2.07 mg/ml (1.92–2.22) at baseline to 4.23 (3.74–4.72), 5.43 (4.84–6.03), 6.37 (5.67–7.07), and 7.58 mg/ml (6.79–8.38) at 8, 12, 32, and 44 months after randomization, respectively (*p* value for time interaction < 0.0001). At 44 months, 17.9% (152/849) of the cohort had methacholine PC₂₀ values greater than 12.5 mg/ml (the cutoff point above which subjects were excluded from entry into the study). Using standard repeated-measures data analysis methodology (16), we assessed the stability of the relationships between parental history and airway responsiveness. As previously described (6), randomization to inhaled budesonide was strongly associated with improvement in PC₂₀, with a mean PC₂₀ of 9.24 mg/ml (95% CI, 7.63–10.84) at the end of the trial for those randomized to inhaled budesonide, compared with 6.87 mg/ml (95% CI, 5.97–7.77) for those not randomized to budesonide (adjusted *p* < 0.0001). Strong associations with methacholine log_ePC₂₀ were also observed for the following covariates: sex, age at randomization, baseline log_e total serum IgE, baseline lung function, history of hay fever or atopic dermatitis, and history of maternal smoking during pregnancy. After adjustment for these covariates, significant and stable associations were observed between log_ePC₂₀ and paternal (but not maternal) history of asthma (Table 3, Models 3 and 4). These results were not appreciably changed by additional adjustment for maternal history of asthma and parental atopy (Table 3, Model 2). These results were reproducible at all time points, and no significant change in the relationships of paternal history of asthma with AHR was observed (i.e., there was no evidence of a time-dependent effect). There was no significant association between either paternal or maternal history of atopy and AHR in the longitudinal analysis (Table 3, Models 5 and 6). Similar to the prerandomization relationships, children with two parents with asthma tended to have greater airway responsiveness compared with those with only one parent with asthma, although this trend did not reach statistical significance (Table 3, Model 1). As noted above, a significant relationship between paternal history of asthma was observed with the baseline FEV₁/FVC ratio. However, unlike the associations with methacholine responsiveness, a longitudinal analysis of the relationship between parental history of asthma and repeated measures of FEV₁/FVC ratio revealed that the baseline association between paternal history of asthma and the FEV₁/FVC ratio did not persist over the 4.5 years of observation (data not shown), suggesting that a paternal history of asthma preferentially influences the airway responsiveness phenotype.

At 44 months after randomization, only 10.7% (18/168) of children with a paternal history of asthma had methacholine PC₂₀ measurements greater than 12.5 mg/ml, compared with 20.0% (126/631) of those without a paternal history (adjusted odds ratio [OR] for likelihood of PC₂₀ > 12.5 mg/ml, 0.48; 95% CI for OR, 0.27–0.85; *p* = 0.01). Children with a maternal

TABLE 1. BASELINE CHARACTERISTICS OF CHILDHOOD ASTHMA MANAGEMENT PROGRAM COHORT AND RELATIONSHIP TO $\log_e PC_{20}$

Variable*	Median PC_{20} at Baseline (IQR)	p Value†
Sex		
Male (n = 621)	1.05 (0.50–2.48)	0.42
Female (n = 420)	1.17 (0.50–2.89)	
Race		0.71
White (n = 711)	1.10 (0.49–2.82)	0.25
Black (n = 138)	1.05 (0.54–2.23)	
Hispanic (n = 98)	1.12 (0.53–2.44)	
Other (n = 94)	0.95 (0.47–2.53)	
Age at randomization, yr		0.25
5–6 (n = 161)	0.98 (0.50–2.13)	
7–8 (n = 294)	1.13 (0.56–2.88)	
9–10 (n = 309)	1.18 (0.54–2.92)	
11–13 (n = 277)	1.02 (0.44–2.72)	< 0.0001
Clinic		
Albuquerque (n = 121)	0.93 (0.34–2.70)	
Baltimore (n = 128)	0.89 (0.50–2.14)	
Boston (n = 124)	1.09 (0.51–3.04)	
Denver (n = 144)	1.72 (0.94–4.41)	
San Diego (n = 122)	0.92 (0.44–1.91)	
Seattle (n = 144)	0.67 (0.32–1.77)	
St. Louis (n = 133)	1.52 (0.62–4.05)	
Toronto (n = 125)	1.14 (0.62–2.64)	
Asthma severity		< 0.0001
Mild (n = 498)	1.3 (0.59–3.34)	
Moderate (n = 543)	0.91 (0.41–1.97)	0.0008
Hay fever for 2 consecutive yr		
Missing (n = 5)	0.35 (0.19–0.38)	
No (n = 479)	1.21 (0.57–2.97)	
Yes (n = 557)	0.99 (0.45–2.46)	0.06
Atopic dermatitis for 2 consecutive yr		
Missing (n = 1)	0.11 (0.11–0.11)	
No (n = 742)	1.12 (0.52–2.70)	
Yes (n = 298)	1.02 (0.48–2.49)	< 0.0002
Parental history of asthma		
Missing (n = 69)	1.25 (0.52–2.89)	
Neither parent (n = 545)	1.17 (0.55–2.92)	
One parent (n = 384)	1.02 (0.48–2.39)	0.42
Both parents (n = 43)	0.52 (0.27–1.13)	
Annual household income		
Missing (n = 41)	0.72 (0.39–2.16)	
< \$30,000 (n = 242)	1.11 (0.48–2.97)	
≥ \$30,000 (n = 758)	1.10 (0.50–2.59)	

Quantitative Variable at Baseline	Median Value (IQR)	Spearman Correlation with $\log_e PC_{20}$	p Value*
Prebronchodilator FEV ₁ , L	1.58 (1.30–1.93)	0.16	< 0.0001
Prebronchodilator FEV ₁ /FVC ratio, absolute	80 (75–86)	0.36	< 0.0001
Total serum IgE level, ng/ml	433 (173–1,221)	–0.32	< 0.0001

Definition of abbreviations: IQR = interquartile range; PC_{20} = provocative concentration of methacholine causing a 20% fall in FEV₁.

* Baseline methacholine PC_{20} measurements were not available for four individuals. These four individuals are included among the counts of individuals in each category of variable to provide an accurate demographic profile of the cohort, but do not contribute to the calculated median values of baseline PC_{20} .

† p values for univariate linear regression with $\log_e PC_{20}$ as the dependent variable.

history of asthma had methacholine PC_{20} measurements that were similar to those without maternal history of asthma (19.3 vs. 17.5%, $p = 0.75$). Parental history of atopy (either maternal or paternal) was not significantly associated with methacholine $\log_e PC_{20}$ over the 44-month period of observation.

DISCUSSION

Although several groups have demonstrated that parental history of asthma affects airway responsiveness in children (7–11), our findings are the first to suggest that a parental history of asthma influences the natural history of airway responsiveness among children with established asthma, and that the father's

asthma history may be the predominant familial determinant of this relationship. We further show that these effects are independent of other known determinants of airway responsiveness and asthma severity, including the baseline atopic state of the child (represented by total circulating IgE level), environmental tobacco smoke exposure, and socioeconomic and demographic factors. Moreover, this relationship persisted over the approximately 4 years of observation and was not modified by the administration of corticosteroids, suggesting that genetic factors influence the natural history of AHR, even in the face of important environmental modifiers.

A large number of studies have evaluated parent-of-origin effects on the development of asthma and allergic susceptibility

TABLE 2. CROSS-SECTIONAL RELATIONSHIP BETWEEN PARENTAL HISTORY OF ASTHMA AND ATOPY WITH $\log_e PC_{20}$ BEFORE RANDOMIZATION

Variable	Median PC_{20} (IQR)	Unadjusted p Value	Adjusted p Value*		
			Model 1	Model 2	Model 3
No. parents with asthma		0.0002	0.003	0.009	0.02
None (n = 545)	1.17 (0.55–2.92)				
One parent (n = 384)	1.02 (0.48–2.39)				
Both parents (n = 43)	0.52 (0.27–1.13)				
Maternal history of asthma		0.30	0.48	0.82	0.68
No (n = 750)	1.12 (0.53–2.61)				
Yes (n = 262)	1.02 (0.43–2.52)				
Maternal history of atopy		0.60	0.91	—	—
No (n = 533)	1.13 (0.49–2.90)				
Yes (n = 487)	1.08 (0.51–2.46)				
Paternal history of asthma		0.001	0.006	0.03	0.06
No (n = 763)	1.13 (0.52–2.95)				
Yes (n = 208)	0.84 (0.41–1.73)				
Paternal history of atopy		0.21	0.34	—	—
No (n = 581)	1.08 (0.50–2.96)				
Yes (n = 371)	1.03 (0.49–2.11)				

For definition of abbreviations, *see* Table 1.

* Model 1 adjusted for age, sex, ethnicity, household income, clinic, baseline total IgE level, and history of hay fever. Models 2 and 3 include additional adjustment for baseline prebronchodilator FEV₁ and prebronchodilator FEV₁/FVC ratio, respectively.

in offspring. There is strong evidence that a maternal history of allergic disease has more influence than paternal history over subsequent allergic phenotypes in offspring (18–20), and several birth cohort studies have demonstrated that maternal but not paternal history of asthma was an important predictor of subsequent wheeze in early childhood (21–23). Maternal history of asthma also appears to modify the effects of environmental factors that promote the development of asthma (24, 25). Given this large body of evidence that the maternal history of asthma predominates over paternal history as a determinant of asthma and atopy, our findings of a predominant paternal influence on the natural course of established AHR may seem contradictory. Although patterns of inheritance of the determinants of airway responsiveness may be different from those factors that modify the expression of this trait over time, there is a growing body of evidence (including data regarding recently described molecular determinants of asthma) suggesting that paternally derived genetic effects play a critical role in the pathobiology of airway responsiveness. Several groups have demonstrated that parental history of asthma is strongly associated with greater airway re-

sponsiveness in offspring (9–11), but these studies did not look for parent-of-origin effects. In a fourth study measuring airway responsiveness in children aged 8 to 11 years and in both parents, AHR in a parent was associated with a twofold increased risk of AHR in the child (26). Risk was similar for both fathers and mothers, with a similar degree of parent-child PC_{20} correlation ($R = 0.14$ father-child, $R = 0.10$ for mother-child; both $p < 0.01$). More recently, however, Kurzius-Spencer and colleagues (27) demonstrated a strong father-offspring (particularly father-son) correlation in airway responsiveness among children. In that study, no mother-offspring correlation in airway responsiveness was found. Additional studies examining the effect of parental history of asthma on subsequent childhood wheeze have demonstrated equal and additive contributions from both parents (28, 29) or a stronger role of paternal history of asthma (30). Dold and colleagues (30) demonstrated that, although children aged 9 to 11 years with a maternal history of asthma had a 1.5-fold increased risk of wheezy bronchitis, a paternal history of asthma had much greater impact, with a relative risk of 4.4.

There is also evidence that the paternal influence increases

Figure 1. Longitudinal relationships between familial history of asthma and $\log_e PC_{20}$ in the Childhood Asthma Management Program. Vertical line denotes time of randomization.

TABLE 3. LONGITUDINAL RELATIONSHIPS BETWEEN PARENTAL HISTORY OF ASTHMA AND ATOPY WITH log_ePC₂₀ DURING THE CHILDHOOD ASTHMA MANAGEMENT PROGRAM

Model	Effect	β-Estimate (SE)	p Value
1	No. parents with asthma		0.06
	One parent	−0.10 (0.08)	
	Both parents	−0.40 (0.18)	
2	Father asthma	−0.21 (0.09)	0.02
	Mother asthma	−0.08 (0.09)	0.38
	Father atopy	−0.09 (0.08)	0.29
	Mother atopy	0.02 (0.08)	0.77
3	Father asthma	−0.21 (0.09)	0.02
4	Mother asthma	0.00 (0.08)	0.99
5	Father atopy	−0.09 (0.08)	0.22
6	Mother atopy	0.00 (0.07)	0.99

Definition of abbreviation: PC₂₀ = provocative concentration of methacholine causing a 20% fall in FEV₁.

All models adjusted for age, sex, race, *in utero* smoke exposure, baseline log_e (total IgE) and FEV₁/FVC ratio, treatment group, clinic, hay fever, and atopic dermatitis. Models differ in which family history covariates are added: Model 1 includes indicator variables for one or two parents with asthma; Model 2 includes dichotomous variables for paternal and maternal histories of asthma and paternal and maternal histories of atopy; Models 3–6 include each of the four parental histories included in Model 2 as separate effects. β-Effect estimates provided for log_ePC₂₀ at 8-month visit. Similar estimates obtained at visits at 20, 32, and 44 months.

with increasing age. Although maternal asthma (not paternal) appears to be an important determinant of childhood wheeze before age 6 (21–23), Litonjua and colleagues (31) demonstrated that paternal contributions to risk of childhood asthma had greater influence among older children. Although maternal history of asthma was associated with childhood asthma at all ages (adjusted OR, 4.1; 95% CI, 1.7–10.1), a paternal history of asthma had an increasing effect over time (adjusted OR, 2.7; 95% CI, 1.0–7.2 over all ages, compared with adjusted OR, 4.1; 95% CI, 1.0–16.0, for children 5 years old). In the Kurzius-Spencer study demonstrating strong father–child (but not mother–child) correlation in AHR, the mean age of the offspring was 21.5 years. The children studied in the Dold study, demonstrating increased risk of asthma among those with a paternal history of asthma, were also older (ages 9–11). These observations are consistent with those in the current study, where all children enrolled in CAMP were at least 5 years old.

There are several biological explanations for parent-of-origin effects, including exclusive exposure to maternal genetic or environmental factors during fetal development, differences in shared postnatal environmental exposures (including exposure to breast milk), hormonal differences, and genetic imprinting, where genetic factors exert their effects depending on whether they were inherited from the mother or father. Maternal influences can exert their effects through all of these mechanisms, whereas traits for which the paternal effects predominate are likely mediated either by hormonal mechanisms or through imprinting. It is also possible that a paternal (more so than maternal) history of asthma differentiates genetic from primarily environmental causes of asthma: the age of onset of asthma is earlier in boys (and therefore in fathers) than in girls (32, 33), suggesting that there is perhaps a stronger impact of genetic factors on asthma development in boys than in girls. Because detailed parental phenotype data (including parental age of asthma onset) are not available in our study, we are unable to test this hypothesis directly. As described above, it is evident from previous studies that both maternal and paternal histories of asthma confer an increased risk for the development of asthma, suggesting

that asthma in both sexes is influenced by genetic factors, and that paternal versus maternal histories of asthma alone do not discriminate predominantly genetic from predominantly environmental asthma. It is quite likely, though, that disease susceptibility genes exert sex-specific effects (32, 34), and that perhaps our observation of a greater paternal influence on the development of AHR relate to AHR-specific genes that are expressed more in males.

Recent advances in the identification of asthma-susceptibility genes may provide some insights into the molecular mechanisms behind our observations of paternal influence on airway responsiveness. In 2002, Leaves and colleagues (35) demonstrated that a region of chromosome 7p is tightly linked with AHR in an Australian population. Further analysis revealed that the linkage signal was essentially restricted to siblings sharing alleles inherited from fathers, not from mothers, suggesting that paternally derived alleles at this locus affect airway responsiveness. Subsequently, a gene mapping to this region (GPRA) was identified as an important asthma-susceptibility gene in two populations, with several multilocus haplotypes demonstrating consistent associations with asthma and IgE level in cohorts from Finland and French Canada (36). Although parent-of-origin effects were not presented in that study, it is interesting to speculate that the associated haplotypes may be of paternal origin. We believe that direct testing of this hypothesis in multiple populations is warranted.

Although our findings are supported by the epidemiologic and genetic data presented above, several important limitations of our study warrant consideration. Parental history of asthma was based on responses to questionnaire data, the majority of which were completed by the CAMP participants' mothers, and no clinical evaluation of parental airway responsiveness was made. Although this introduces the possibility of errors in exposure classification and possible reporting bias, Litonjua and colleagues (31) have reported in another study that maternal reports of paternal asthma history were quite reliable, with validation questionnaires completed by fathers confirming the mothers' reports. An additional limitation is that our findings may be valid only among children with established mild to moderate asthma, given that children with severe asthma were not enrolled in CAMP. If maternal influences are important determinants of severe asthma, selection bias may be driving these results. Although this possibility cannot be excluded, it is important to note that the prevalence of maternal asthma (25.9%) was similar to or greater than that found in other studies (22, 23). Differential loss to follow-up is an important cause of spurious association in longitudinal studies. Although subjects lacking AHR measurements at 44 months had a higher frequency of a maternal history of asthma, it is unlikely that differential loss to follow-up explains our findings, primarily because the relationships between parental history of asthma and airways responsiveness were observed at the start of the trial, before loss to follow-up would be an important consideration. Moreover, our primary finding was of a strong relationship between PC₂₀ and paternal history of asthma, which was not a predictor of missing AHR measurements at any visit ($p > 0.36$ for all four visits). Finally, although maternal history of asthma was associated with loss to follow-up at 44 months ($p = 0.02$) and at 32 months ($p = 0.03$), the frequency of maternal history of asthma was similar between those with and without PC₂₀ measurements at earlier visits ($p = 0.25$ at 8 months, $p = 0.83$ at 20 months). The relationship between parental history of asthma and airways responsiveness at these time points were similar to those at baseline and at subsequent visits, again suggesting that subsequent loss to follow-up did not bias our observations. As noted above, there was no change in the relationship of parental history of asthma with AHR over time (i.e., no evidence of a time-by-parental history interaction). To-

gether, these data suggest that differential loss to follow-up does not explain our results.

In conclusion, we have demonstrated that parental history of asthma affects airway responsiveness in children with established asthma, and that these effects persisted over 4 years of observation. Together with recent demonstrations of significant familial resemblance in asthma severity scores (37), these data suggest that genetic factors influence not only the development of asthma-related phenotypes but also the clinical course of disease. We have also provided evidence that the genetic influences on airways responsiveness demonstrate parent-of-origin effects. The recent identification of an asthma-susceptibility gene in a genomic region demonstrating paternal linkage to airway responsiveness suggests that considering parent-of-origin effects in future studies will help facilitate the identification of the genetic determinants of airway responsiveness. To date, linkage analysis has identified four additional loci that appear to harbor AHR quantitative trait loci, including regions of chromosomes 2, 5q, 11q, 12q, and 20p (38–42). Aside from chromosome 20 (ADAM33) (42), the precise identity of the responsible genes remains unknown. Perhaps reanalysis of these linkage results, accounting for parent-of-origin effects (43), may facilitate the identification of these elusive genes.

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