Repeatability of response to asthma medications

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Background: Pharmacogenetic studies of drug response in asthma assume that patients respond consistently to a treatment but that treatment response varies across patients; however, no formal studies have demonstrated this.

Objective: To determine the repeatability of commonly used outcomes for treatment response to asthma medications: bronchodilator response, FEV_1, and PC_{20}.

Methods: The Childhood Asthma Management Program was a multicenter clinical trial of children randomized to receiving budesonide, nedocromil, or placebo. We determined the intraclass correlation coefficient (ICC) for each outcome over repeated visits over a period of 4 years in the Childhood Asthma Management Program by using mixed-effects regression models. We adjusted for the covariates age, race/ethnicity, height, family income, parental education, and symptom score. We incorporated each outcome for each child as repeated outcome measurements and stratified by treatment group.

Results: The ICC for bronchodilator response was 0.31 in the budesonide group, 0.35 in the nedocromil group, and 0.40 in the placebo group, after adjusting for covariates. The ICC for FEV_1 was 0.71 in the budesonide group, 0.60 in the nedocromil group, and 0.69 in the placebo group, after adjusting for covariates. The ICC for PC_{20} was 0.67 in the budesonide and placebo groups and 0.73 in the nedocromil group, after adjusting for covariates.

Conclusion: The within–treatment group repeatability of FEV_1 and PC_{20} is high; thus, these phenotypes are heritable. FEV_1 and PC_{20} may be better phenotypes than bronchodilator response for studies of treatment response in asthma. (J Allergy Clin Immunol 2009;123:385-90.)

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The purpose of research in pharmacogenetics is to identify genetic predictors of individual response to medications.[1] This field assumes response to treatment is consistent for a given individual; however, this assumption has not been studied.[1]

Asthma is a complex chronic condition, and the response to medication for asthma is consequently variable. Multiple studies suggest familial aggregation of asthma, and twin studies suggest the heritability of asthma is between 36% and 70%.[2-4] Asthma-related phenotypes such as pulmonary function as measured by bronchodilator response, FEV_1, and PC20 also appear to be heritable.[5-7] There is a dearth of evidence suggesting treatment response in asthma is heritable, yet this is assumed in pharmacogenetic studies. Asthma pharmacogenetics is a rapidly growing field that has the potential to have profound clinical implications.

For pharmacogenetic studies in asthma to have clinical implications, individuals must respond differently to medications. If variability in therapeutic response has a genetic basis, there must be evidence of both interindividual variation and intraindividual repeatability in response.[7] Many studies have demonstrated interindividual variation in FEV_1 and PC_{20} responses to treatment for asthma.[7-10] Variability in response to β_2-agonists has been known for more than 5 decades,[11] and variability in response to corticosteroids has been demonstrated relatively recently.[9,10,12] To our knowledge, no studies demonstrate intraindividual repeatability in response to asthma medication, yet studies in asthma pharmacogenetics assume that individuals will have consistent response to medications. Longitudinal studies with repeated measures of treatment response may help clarify whether this assumption is true.

Twin studies are the ideal method for studying heritability because monozygotic twins who share 100% of genes have smaller intrapair differences in pulmonary function than dizygotic twins, who share an average of 50% of genes. Unfortunately, conducting twin studies for studying heritability of most classes of drug response is logistically difficult. One way in which heritability may be inferred is by use of the intraclass correlation coefficient (ICC).[13] Determining heritability through repeated measurements has been used extensively in genetic studies of animals,[14,15] and the principles apply to the study of heritability in human beings. Therefore, repeatability studies involving drug treatment response can also take advantage of the ICC. The ICC for medication response compares the variability of the responses within and between individuals over the course of repeated drug administration. ICC is given by $\sigma_b^2/(\sigma_b^2 + \sigma_w^2)$, where σ_b^2 is the between-subject variance and σ_w^2 is the within-subject variance. Although this ICC for medication response does not use family data, by comparing the consistency of

Abbreviations used
CAMP: Childhood Asthma Management Program
ICC: Intraclass correlation coefficient

treatment response over time within an individual to the response between individuals, the ICC does address the proportion of the response that is innate and, therefore, most likely heritable.

The objective of this report is to determine the ICC of bronchodilator response, FEV_1, and PC_{20} over repeated visits while on specific asthma medications in a longitudinal cohort of children with asthma. We hypothesize that the ICC of these outcomes will be high.

METHODS

The Childhood Asthma Management Program is a multicenter trial that enrolled 1041 children between the ages of 5 and 12 years with mild to moderate persistent asthma between 1993 and 1995.[16] Subjects were randomly assigned to receive budesonide, nedocromil, or placebo and were followed for 4 to 6 years every 2 to 4 months to study the long-term use of the medications. Details of this study have been previously published.[16] The institutional review board at each of the 8 participating institutions approved the study, and parents or guardians of the subjects gave informed consent.[16]

Our main outcome measures were the following within treatment group responses: bronchodilator response, prebronchodilator FEV_1, and log PC_{20} over repeated visits in the Childhood Asthma Management Program (CAMP) population.[17] Research assistants obtained spirometry measurements on the subjects both before and after bronchodilator twice yearly. Bronchodilator response was calculated at each visit as FEV_1 ([postbronchodilator FEV_1 –prebronchodilator FEV_1]/prebronchodilator FEV_1). Each year, the subjects' airway responsiveness to methacholine was measured by calculating the concentration of methacholine that caused a 20% decrease in the FEV_1. The concentration that provoked a 20% decrease from postdiluent FEV_1 was obtained by linear interpolation of logarithmic dose-response curve expressed as PC_{20}. We used the outcome measures from randomization to month 48 postrandomization for the outcome variables bronchodilator response, prebronchodilator FEV_1, and log PC_{20}.

With the help of parents or guardians, subjects completed diary cards daily to document recorded night awakenings caused by asthma, morning and evening peak flow readings by a peak flow meter (Assess; HealthScan Products, Cedar Grove, NJ), use of study medication, use of albuterol or prednisone, absences from school because of asthma, visits to providers' offices or hospitals because of asthma, and severity of symptoms. At each study visit, research assistants measured the subjects' height (using a Harpenden stadiometer, Crosswell, United Kingdom) and weight. We divided the weight and height measurements at randomization into internal quartiles of weight and height based on the CAMP population.

We controlled for confounding by considering covariates that could influence the outcomes of bronchodilator response, prebronchodilator FEV_1, and log PC_{20}. Thus, we adjusted for the covariates age at randomization, race/ethnicity, height, family income, parental education, and symptom score. For the outcome of bronchodilator response, we adjusted for prebronchodilator FEV_1. Race/ethnicity, family income, and parental education were determined by parental self-report. Symptom scores were developed on the basis of daily diary measures of symptom control, including symptom frequency, number of asthma episode-free days per month, uses of albuterol for symptoms and to prevent exercise-induced bronchospasm per week, and number of night awakenings per month. Subjects were classified as having mild symptoms if they had fewer than 2 episodes a week of symptoms and moderate symptoms if they had 2 or more episodes per week of symptoms.

Statistical analyses

We used mixed-effects regression models to estimate the ICC for each outcome measure. We incorporated each outcome for each child as repeated outcome measurements and stratified by treatment group using SAS version 9.1 (SAS Institute, Cary, NC). For each outcome, to test the equivalence of ICCs across the 3 treatment groups, we constructed a χ^2 test statistic by using a bivariate vector and its covariance matrix. The entries of the bivariate vector are the differences of ICCs between the groups of budesonide and nedocromil, and the groups of nedocromil and placebo. Then the P values are obtained, assuming the test statistic has an asymptotic χ^2 distribution with 2 degrees of freedom under the null hypothesis.

RESULTS

The median bronchodilator response, prebronchodilator FEV_1, and log PC_{20} values at randomization for each treatment group are presented in Table I. The median bronchodilator response for all subjects was 0.08 at randomization, and this value was similar in each treatment group. Bronchodilator response and log PC_{20} at randomization were not significantly different depending on treatment group, race/ethnicity, sex, mean internal quartiles of weight, mean internal quartiles of height, or parental education. Bronchodilator response was significantly different for household income. The prebronchodilator FEV_1 was significantly different for race/ethnicity, mean internal quartile of weight, and mean internal quartiles of height. Bronchodilator response and log PC_{20} at randomization were significantly different for symptom score. The median bronchodilator response value was 0.09 for subjects with a symptom score indicating moderate symptoms, compared with 0.07 for subjects with mild symptoms. This expected finding occurs because subjects with moderate symptoms start with prebronchodilator FEV_1 values that are lower.

Mean responses for each outcome at visits between randomization and 48 months are depicted in Fig 1. These graphs demonstrate the stability of the mean values with repeated measures over time. The slight increase in slope for the mean values for prebronchodilator FEV_1 is expected because over the course of 48 months, subjects grow in height and weight, leading to increased values of FEV_1. The increase in slope for both prebronchodilator FEV_1 and log PC_{20} could reflect better asthma treatment over time because subjects were seen by their physicians who had the opportunity to make slight changes in medication regimens or as a result of treatment effect, with the placebo group showing a placebo effect.

The ICC values for each outcome are shown in Table II. The ICC for bronchodilator response ranged from 0.31 to 0.40, after adjusting for age, race/ethnicity, height, family income, parental education, and symptom score. The ICC results were the same whether or not we adjusted for covariates. We chose to present the adjusted results to account for nongenetic factors. The ICC for prebronchodilator FEV_1 ranged from 0.60 to 0.71, after adjusting for covariates. The ICC for log PC_{20} ranged from 0.67 to 0.73. According to Rosner,[18] an ICC of less than 0.4 suggests poor reproducibility, an ICC between 0.4 and 0.75 indicates fair to good reproducibility, and an ICC greater than 0.75 suggests excellent reproducibility. Thus, the ICC for bronchodilator response has fair to poor reproducibility, whereas the ICCs for prebronchodilator FEV_1 and log PC_{20} have good reproducibility. The ICCs for prebronchodilator FEV_1 were significantly different ($P = .006$) among the 3 treatment groups, suggesting that the repeatability of prebronchodilator FEV_1 is high, only among subjects in the same treatment group. Similarly, the ICCs for bronchodilator response were also significantly different ($P = .02$) among the treatment groups.

TABLE I. Median values for bronchodilator response, prebronchodilator FEV_1, and log PC_{20} values at randomization, stratified by covariates

		Bronchodilator response		Pre-bronchodilator FEV1 (L)		log PC20 (mg/ml)	
	No.	Median (25%:75%)	*P* value	Median (25%:75%)	*P* value	Median (25%:75%)	*P* value
Treatment group			.61		.90		.59
Budesonide	311	0.08 (0.04:0.15)		1.58 (1.32:1.92)		0.055 (-0.7:0.95)	
Nedocromil	312	0.08 (0.04:0.15)		1.59 (1.28:1.93)		0.09 (-0.66:1.04)	
Placebo	417	0.08 (0.04:0.14)		1.58 (1.315:1.925)		0.09 (-0.71:0.95)	
Race/ethnicity			.46		.0004		.71
Hispanic	97	0.09 (0.05:0.16)		1.7 (-1.39:2.07)		0.11 (-0.64:0.89)	
Black	138	0.1 (0.05:0.16)		1.45 (1.16:1.76)		0.045 (-0.62:0.8)	
White	710	0.08 (0.04:0.15)		1.6 (1.33:1.93)		0.09 (-0.71:1.04)	
Other	94	0.085 (0.04:0.14)		1.56 (1.29:1.91)		-0.05 (-0.75:0.93)	
Sex			.14		.64		.42
Male	620	0.085 (0.04:0.15)		1.6 (1.33:1.93)		0.045 (-0.69:0.91)	
Female	419	0.08 (0.04:0.14)		1.56 (1.28:1.92)		0.16 (-0.7:1.06)	
Weight			.80		<.0001		.69
<25th percentile	247	0.08 (0.04:0.16)		1.19 (1:1.35)		0.07 (-0.82:0.91)	
<50th percentile	268	0.08 (0.04:0.14)		1.48 (1.32:1.67)		0.08 (-0.6:0.86)	
<75th percentile	260	0.08 (0.05:0.15)		1.77 (1.545:1.96)		0.09 (-0.65:1.1)	
≥75th percentile	260	0.08 (0.04:0.14)		2.12 (1.79:2.465)		0.14 (-0.72-1.13)‘	
Height			.85		<.001		.93
<25th percentile	254	0.08 (0.04:0.14)		1.17 (1:1.33)		0.12 (-0.7:0.86)	
<50th percentile	259	0.08 (0.04:0.15)		1.44 (1.32:1.62)		0.09 (-0.59:0.95)	
<75th percentile	258	0.08 (0.04:0.15)		1.765 (1.59:1.91)		0.055 (-0.755:1.04)	
≥75th percentile	258	0.09 (0.05:0.15)		2.185 (1.91:2.48)		0.085 (-0.76:1.13)	
Household income			.04		.56		.53
<$30,000	241	0.09 (0.04:0.16)		1.57 (1.27:1.91)		0.105 (-0.74:1.09)	
≥$30,000	757	0.08 (0.04:0.14)		1.59 (1.32:1.93)		0.09 (-0.69:0.95)	
Parental education			.27		.85		.87
High school or less	185	0.08 (0.04:0.13)		1.59 (1.31:1.93)		0.04 (-0.64:1.03)	
Some college	853	0.08 (0.04:0.15)		1.58 (1.3:1.92)		0.09 (-0.71:0.97)	
Symptom score			<.001		.38		<.0001
Mild	496	0.07 (0.04:0.13)		1.56 (1.29:1.91)		0.26 (-0.525:1.205)	
Moderate	543	0.09 (0.05:0.17)		1.62 (1.33:1.94)		-0.09 (-0.88:0.68)	

DISCUSSION

This report has 3 key findings. First, we found that FEV_1 and log PC_{20} within each treatment group have high correlation within subjects over time, which suggests that these phenotypes have high repeatability and heritability. Second, within-subject repeatability is high for the phenotypes of prebronchodilator FEV_1 and log PC_{20} regardless of age, sex, race/ethnicity, and symptom score. Finally, the ICC is treatment-specific.

The finding that prebronchodilator FEV_1 and log PC_{20} within each treatment group have high repeatability is consistent with findings in previous studies. For example, FEV_1 has been shown to help classify asthma severity,[19] predict risk of asthma exacerbations,[20] and predict future FEV_1,[21] suggesting high intraindividual correlation. Similarly, PC_{20} has been demonstrated to predict future lung function.[21] In addition, studies suggest high intraindividual response to inhaled steroids.[9,10,12] The ICCs in this report can be interpreted in the context of other studies finding that the correlation coefficient of blood pressure between initial and subsequent measures is between 0.3 and 0.7[22] and the ICC for height is 0.96 and for weight is 0.88.

Bronchodilator response appears to have fair to poor repeatability and heritability, yet many studies in asthma pharmacogenetics use bronchodilator response as an outcome. One reason for this low repeatability is that bronchodilator response is calculated through 2 FEV_1 measurements, prebronchodilator and postbronchodilator; thus, there is a higher likelihood of variability. In addition, although trained research assistants conducted the spirometry measurements and administered the bronchodilator, technical factors in measurements could have decreased reproducibility of bronchodilator response. Furthermore, the group receiving budesonide had lower ICC (0.31) than the nedocromil (0.35) and placebo (0.40) groups, likely because budesonide has anti-inflammatory functions that had more of an influence on prebronchodilator FEV_1 and less on the postbronchodilator FEV_1. Similarly, nedocromil has mild anti-inflammatory functions that may have contributed to the ICC that was lower than the placebo group yet higher than the budesonide group.

The ICC values did not change significantly after adjusting for age, sex, race/ethnicity, and symptom score, lending further support to the hypothesis that bronchodilator response, FEV_1, and PC_{20} are heritable. We adjusted for these covariates to account for other nongenetic factors, but they did not appear to play a role.

For each outcome, the ICC varied between treatment groups, with the highest ICC for the bronchodilator response related to no active anti-inflammatory medications, and the highest ICC for FEV_1 noted in the inhaled corticosteroid group. These treatment-specific findings could be explained by effect modification or gene by environment interactions. For example, anti-

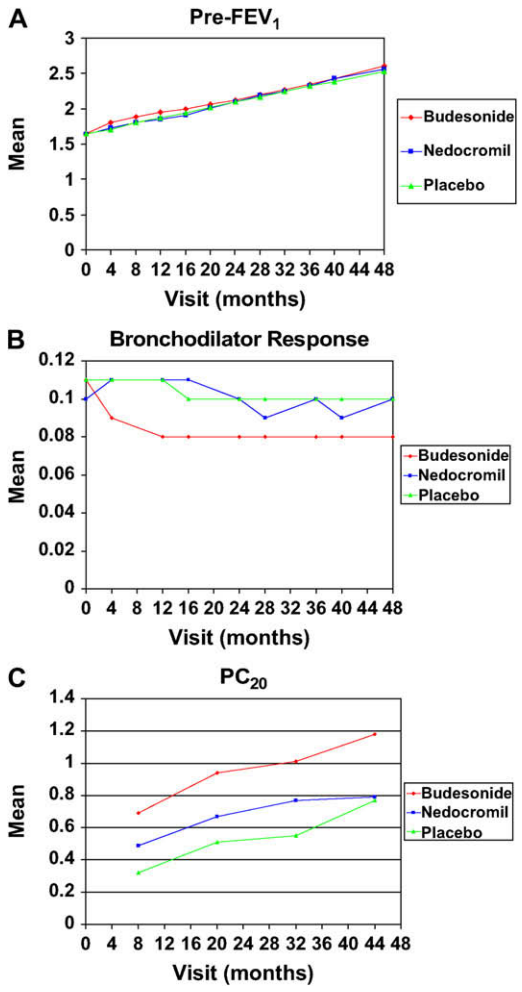

FIG 1. Mean responses for each outcome at visits between randomization and 48 months, stratified by treatment group. **A,** Prebronchodilator FEV_1. **B,** Bronchodilator response. **C,** Log PC_{20}.

inflammatory medications alone or interactions between anti-inflammatory medications and genetic factors could act as effect modifiers of bronchodilator response.

Strengths of this report include a well characterized multicenter cohort, the ability to control for multiple confounders, and availability of repeated outcome measurements over several years. To our knowledge, this is the first report to examine the repeatability of response to asthma medications. The findings in this report suggest that studies of the genetics of response to asthma medications could use bronchodilator response as an outcome measure, but prebronchodilator FEV_1 and PC_{20} may be even better outcome measures. Despite these strengths, these findings were in 1 cohort of children ages 5 to 12 years who were followed for 4 years, which may limit the generalizability of our findings. In addition, our assessment of repeatability approximates heritability, but the gold standard method for assessing heritability is through studies of twins.

In conclusion, intraindividual response to asthma medications is high, suggesting that response to asthma medications has a genetic basis. Our findings of high repeatability for FEV_1 and PC_{20} suggest high heritability; thus, FEV_1 and PC_{20} are good phenotypes for asthma pharmacogenetic studies.

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TABLE II. ICC values for bronchodilator response, prebronchodilator FEV_1, and log PC_{20} after adjusting for age, race/ethnicity, height, family income, parental education, and symptom score

	Bronchodilator response		Prebronchodilator FEV_1		Log PC_{20}	
	ICC (95% CI)	*P* value	ICC (95% CI)	*P* value	ICC (95% CI)	*P* value
Budesonide	0.31 (0.26-0.36)	.02	0.71 (0.67-0.75)	.006	0.67 (0.63-0.72)	.11
Nedocromil	0.35 (0.31-0.40)		0.60 (0.56-0.65)		0.73 (0.68-0.77)	
Placebo	0.40 (0.36-0.44)		0.69 (0.66-0.72)		0.67 (0.62-0.71)	

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Clinical implications: Response to asthma medications appears to have a genetic basis. Thus, development of pharmacogenetic tests in asthma is possible.

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