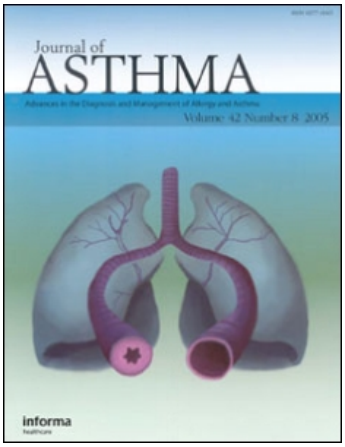

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Polymorphism of the *ADRB2* Gene and Response to Inhaled Beta- agonists in Children with Asthma: A Meta-analysis

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ORIGINAL ARTICLE

Polymorphism of the *ADRB2* Gene and Response to Inhaled Beta- agonists in Children with Asthma: A Meta-analysis

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Background. About 9% of children have asthma, corresponding to almost 6.8 million children in the USA and 1.1 million in the UK. Asthma exacerbations are the leading cause of pediatric emergency room visits and impose a large burden on the individual, family, and society. There is mounting evidence that therapeutic failure of inhaled beta-agonists is associated with polymorphisms of the β_2-adrenergic receptor gene (*ADRB2)*; specifically, mutations leading to amino acid changes at positions 16 and 27, which alter down-regulation of the β_2-adrenergic receptor (β_2AR), induce resistance to the smooth-muscle relaxing effect of β_2-adrenergic agonists. *Methods*. We conducted a meta-analysis to examine the association between *ADRB2* polymorphisms and the response to inhaled β_2-adrenergic agonists in children with asthma. We included all published studies until November 2008, in which asthmatic children underwent testing for acute bronchodilator response, defined as $\geq$ 15% improvement in forced expiratory volume in 1 second (FEV_1) and single nucleotide polymorphism (SNP) genotyping for positions 16 and/or 27 of the β_2AR. Individual and summary odds ratios were calculated using a random effects model. *Results*. We identified three case-control or family-based studies involving 960 asthmatic children (692 children with negative β_2-bronchodilator response, defined as $<$ 15% improvement in FEV_1 and 268 children with positive bronchodilator response). We found a significant association between favorable therapeutic response to inhaled β_2-adrenergic agonists in asthmatic children and the Arg/Arg phenotype at position 16 of the β_2AR [OR = 1.77; 95% CI (1.01; 3.1); $p = 0.029$], compared with the Arg/Gly or Gly/Gly phenotypes. The beneficial effect of Arg at position 16 of the β_2AR was most pronounced in African-American asthmatic children [OR = 3.54; 95% CI (1.37, 9.13)]. There was no association between clinical response to β_2-agonists and polymorphism at amino acid position 27 of the β_2AR (OR = 1.04; 95% CI [0.76,1.42]). *Conclusions*. Failure of bronchodilator response to inhaled beta-agonists in asthmatic children is associated with the Gly allele (Arg/Gly and Gly/Gly genotypes) at position 16 of the β_2-adrenergic receptor. Genetic typing for β_2AR polymorphism may help identify children with drug-resistant asthma.

Keywords β_2-adrenergic receptor (β_2AR); polymorphism; asthma; meta-analysis; children

INTRODUCTION

Asthma affects almost 6.8 million children currently in the US and 1.1 million in the UK. It accounts for nearly 500,000 hospitalizations, 2 million emergency department visits, about 10,000 pediatric intensive care unit admissions, and 5,000 deaths in the United States each year (1–3). Similar data on the "soaring" prevalence of asthma in children have been reported in the UK, with an estimated prevalence of 1 in 9 (4), and the total cost of asthma to the UK economy exceeds £2.3 billion a year. Despite some advances in treatment, the burden of asthma on the child, family, and society is significant. Visits to the doctor because of asthma have more than doubled in the last decade (3). The succeeding short-term outcome of asthma is poor, including persistence of symptoms and school absenteeism (5). Furthermore, two thirds of children with asthma have to limit their daily activities because of uncontrolled disease (6).

The mainstay of treatment of acute asthma in children includes inhaled short-acting β_2-adrenergic receptor (β_2AR) agonists, such as albuterol, but response is highly variable and difficult to predict (7). Response is influenced by several clinical factors, such as age, disease severity, and environmental exposures (7, 8), but these do not provide a mechanistic explanation for drug resistance.

Polymorphisms in the β_2AR gene (Human Genome Organization nomenclature [HUGO] name, *ADRB2*) are a potential mechanism of resistance to β_2-agonists, and the β_2AR gene is the most widely studied candidate gene (2,7,9–16). The β_2AR gene is located on chromosome 5q31.32 (17). Several point mutations in the β_2AR gene have been described; of these, two are more frequent and result in amino acid exchanges in the extracellular amino-terminus of the receptor (15). These two functionally relevant mutations are responsible for the exchanges arginine 16 to glycine (Arg16Gly) and glutamine 27 to glutamic acid (Gln27Glu). Polymorphic changes in these two positions in the β_2AR result in normal agonist binding and G_s coupling but subsequently altered down-regulation of the receptor (18, 19).

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†We dedicate this manuscript in memory of the lead investigator, a great mentor, researcher and clinician, Dr. Michael W. Shannon, who passed away during this study.

There is mounting evidence that polymorphisms in the β_2AR gene are associated with significant variability in response to short-acting β_2-agonists (SABA) and that a subset of patients with certain genotypes do not respond favorably to inhaled SABA (2,16). In adults, genetic variations in this receptor have also been linked to asthma severity (20), bronchial hyper-responsiveness (21), and lung function tests (22). Previous attempts (2,7,9–14) to link β_2AR gene polymorphisms to response to SABA in asthmatic children were under-powered and therefore could not define the strength of this relationship. Various studies have used different outcome measures and have produced discordant findings.

We conducted a systematic review and meta-analysis of all relevant published studies to determine the role of single nucleotide polymorphisms (SNPs), affecting amino acid sequence at position 16 and 27 in the β_2AR, in the acute response of asthmatic children to inhaled β_2-agonists.

Methods

We searched MEDLINE and EMBASE from January 1966 through November 2008 to identify all published studies that reported the genotypes for the arginine 16 to glycine (Arg16Gly variant) and glutamine 27 to glutamic acid (Gln27Glu variant) polymorphisms in the β_2AR gene among asthmatic children with responsive and refractory disease. The Boolean search strategy "asthma AND (polymorphisms OR pharmacogenetics) AND children AND adrenergic receptor" was used. Relevant articles were retrieved with no language restrictions. In addition, the reference lists of all pooled articles were carefully scrutinized for additional relevant publications. Published meeting abstracts and proceedings were also searched between January 1980 and November 2008 using Scopus conference proceedings and Web of Knowledge databases for studies in progress or studies not yet published in the peer–reviewed literature. As appropriate, additional data, including ethnic stratification of study participants, were requested from the original authors.

Studies were included if they were case-control or cohort studies and included data on the frequency of Arg16Gly or/and Gln27Glu mutations in asthmatic children and their correlation with SABA-responsive and SABA-resistant disease. Papers that defined response as an increase over 15% in FEV_1 after SABA use compared to baseline, which is an accepted, clinically relevant improvement (13, 16), were included in the study. Two experienced investigators independently selected studies for inclusion in the meta-analysis, based on the presented inclusion criteria and using a standardized checklist. They received only the "Methods" sections and were blinded to authors' names, journal titles, and publication dates. The study reviewers were forwarded the selected articles and independently extracted relevant data from the results sections into 2×2 contingency tables. The extracted data were entered into Cochrane's Review Manager Software (version 4.1, Oxford: Cochrane Collaboration). Individual and summary odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using a random effects model. Included studies were tested for heterogeneity using the chi-square test and the I^2.

Results

Ten publications were retrieved for review (2,7,9–14,16,23). Three studies (11,13,16) (one conducted in the US and Canada, one in the US, and the third in China) were identified as suitable for the meta-analysis by both reviewers. Two articles reported case–control studies (11,13), and the third (16) was a family-based study that reported on the genetic analysis of participants in the Childhood Asthma Management Program (CAMP) (24). All included studies focused on the prevalence of position 16 (i.e., Arg/Arg, Arg/Gly or Gly/Gly) and/or 27 alleles (i.e., Glu/Glu, Glu/Gln or Gln/Gln) and their relation to acute bronchodilator response to SABA in asthmatic children.

A total of 960 asthmatic children were included in the 3 studies, involving 692 children with negative β_2-bronchodilator response and 268 children with positive bronchodilator response (Table 1). In the pooled analysis (Figure 1), we identified a significant association between anti-asthmatic drug resistance and a β_2AR polymorphism. We found an association between favorable therapeutic response to inhaled β_2-adrenergic agonists in asthmatic children and the Arg/Arg genotype at position 16 of the β_2AR (OR = 1.77; 95% CI (1.01; 3.1); [Random Effects Model]; $p = 0.029$) compared with the Arg/Gly or Gly/Gly genotypes (Figure 1). The beneficial effect of Arg at position 16 of the β_2AR was most pronounced in African-American asthmatic children (OR = 3.54; 95% CI [1.37, 9.13]; Table 1). We found no association between polymorphisms at position 27 of the β_2AR and response to inhaled β_2-adrenergic agonists in asthmatic children (OR = 1.04; 95% CI [0.76,1.42]; Figure 2).

Discussion

In this meta-analysis of observational case-control and family-based studies involving 960 children with asthma, we found an association between the Gly allele (Arg/Gly and Gly/Gly genotype) at position 16 of the β_2AR and resistance to the bronchodilator effect of inhaled short-acting β_2-agonists. Patients who responded favorably to SABA were more likely to have the Arg/Arg variant at position 16 of the β_2AR. That effect was most consistent in African-American children.

Per design, we included studies involving asthmatic children exclusively because asthma pathogenesis in adult patients tends to differ from that of children and often involves chronic components, such as chronic obstructive pulmonary disease, industrial and workplace exposures, and long-term cigarette smoking. These variables may significantly compromise the response to SABA in acute asthmatic attacks, regardless of the patient's genotype. They can attenuate the smooth–muscle relaxation effect induced by SABA, interfering with our ability to quantify the role of receptor pharmacogenetics on clinical response.

We conducted a systematic review and meta-analysis of all relevant studies, as the number of patients in isolated pediatric studies did not allow drawing a definitive conclusion regarding this common clinical problem. We chose to explore changes in FEV_1 after SABA nebulizations as the main outcome measure because this was the most objective, immediate, and most common endpoint studied by other groups. Importantly, it is unlikely that publication bias plays a role or could lead to overestimation of the true effect size of this finding since the original reported observations (signal)

TABLE 1.—List of articles included in the meta-analysis and raw data extracted. Individual and summary odds ratios were calculated using a random effects model.

Paper	Responsive			Non Responsive			Meta analysis			Responsive			Non Responsive			Meta analysis		
	Genotype Arg/Arg	SNP 16 Gly/Gly or Arg/Gly	total responsive	Genotype Arg/Arg	SNP 16 Gly/Gly or Arg/Gly	total Non responsive	OR	SNP 16 (lower 95% CI)	(upper 95% CI)	Genotype Gln/Gln	SNP 27 Gln/Glu or Glu/Glu	total responsive	Genotype Gln/Gln	SNP 27 Gln/Glu or Glu/Glu	total Non responsive	OR	SNP 27 (lower 95% CI)	(upper 95% CI)
Martinez et al. (1997)	3	7	10	2	26	28	5.57	0.77	40.12	5	5	10	11	17	28	1.55	0.36	6.61
Fu et al. (2002)	15	34	49	7	18	25	1.13	0.39	3.29	39	10	49	18	7	25	1.52	0.5	4.63
Silverman et al. (2003) - Caucasian cohort	50	102	152	190	297	487	1.13	0.7	1.85	50	96	146	158	326	484	1.07	0.73	1.59
Silverman et al. (2003) - African American cohort	7	25	32	32	61	93	3.54	1.37	9.13	19	13	32	64	30	94	0.69	0.3	1.57
Silverman et al. (2003) - Hispanic cohort	9	16	25	20	39	59	2.01	0.62	6.57	12	14	26	28	31	59	0.95	0.38	2.39
Summary							1.77	1.01	3.1							1.04	0.76	1.42

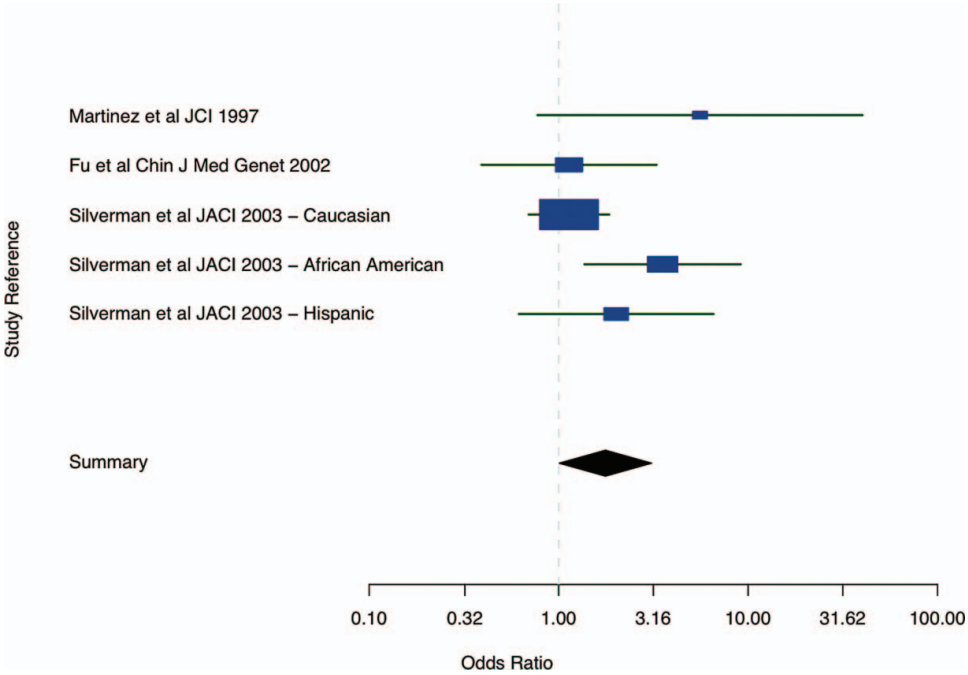

FIGURE 1.—Metaanalysis plot of the association between SNP16 and response to β_2-agonists in children. Summary OR = 1.77 95% CI (1.01, 3.1).

were more modest than those reported by subsequent, larger studies. Several relevant studies used different endpoints and therefore could not be included in the present meta-analysis. The excluded articles (2,7,9,10,12,14,23) used various outcome measures to assess drug-responsiveness, such as long-term bronchodilator response after chronic use (12), use of long-acting inhaled β_2-agonists (14), usage of asthma scores that do not include FEV_1 measurements (2), their patients had underlying chronic lung disease (23), or investigators used stretch-out times between inhalations (7) or did not report extractable dichotomous data (9).

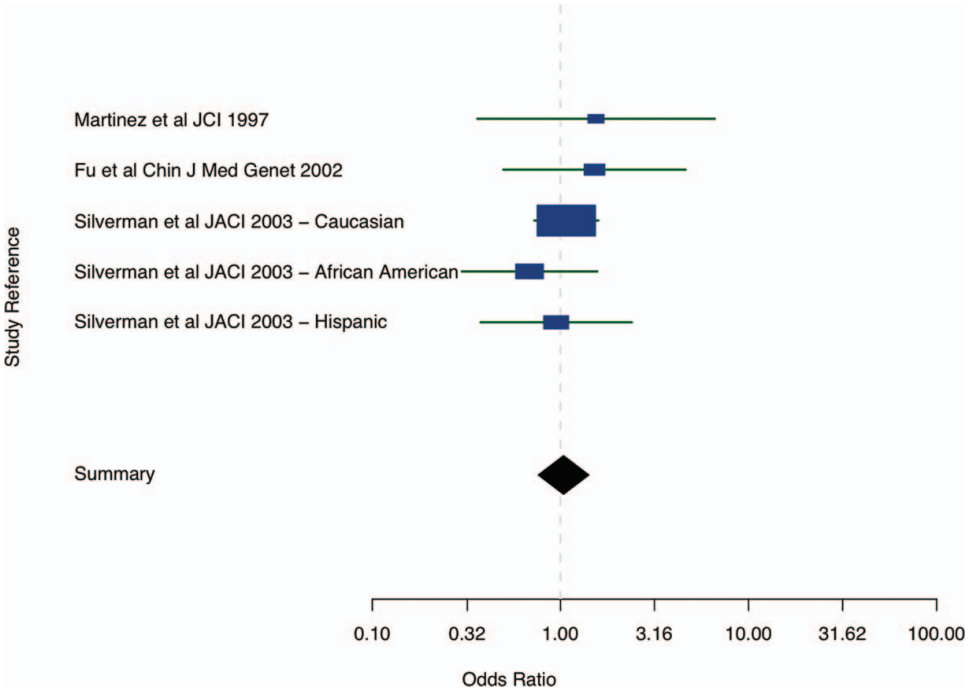

FIGURE 2.—Metaanalysis plot of the association between SNP27 and response to β_2-agonists in children. Summary OR = 1.04 95% CI (0.76, 1.42).

The association between *ADRB2* genotypes and response to inhaled β_2 agonists has been controversial, and discordant findings have been reported. Some authors have found that the Arg/Arg genotype at position 16 is associated with favorable response to SABA (13,25,26), while others reported the opposite (27–33). A similar picture was obtained by groups studying polymorphic genotypes at position 27 of the β_2AR or combinations of the two sites (haplotypes). For example, after use of a bronchodilator for 4 weeks, homozygotes for Gln27 had a decline in bronchodilator response, but there was no such difference for the Arg16 codon (12). In managing acute asthma, Glu27 homozygotes responded most rapidly to treatment with salbutamol, but there was no correlation of clinical response with position 16 (7). In pediatric patients with cystic fibrosis, there was no significant association between positive bronchodilator response and either the 16 or 27 codons (23). In a recent study of 37 children with severe asthma admitted to ICU, Gly/Gly genotype at position 16 was associated with shorter length of stay and duration of continuously nebulized β_2-agonists, compared with children with the Arg/Arg or Arg/Gly genotypes (2). However, the present meta-analysis, as well as the majority of both pediatric and adult studies not included in the meta-analysis (25,26), found that the Gly/Gly genotype at position 16 is significantly associated with decreased response to β_2-agonists.

The pronounced association between the Gly allele at position 16 of the β_2AR and therapeutic failure of β_2 agonists in African-American asthmatic children is of particular relevance. Genetic variation may explain the increased risk for asthma-related deaths and adverse events found in African-American subjects treated with long-acting β-agonists in the SMART Trial (34). These observed adverse events led to a subsequent FDA black box warning regarding long-acting β-agonists in asthma. In addition to our findings, an association between the Arg-19Cys polymorphism in the β_2AR and response to albuterol was found in an African-American population consisting of both pediatric and adult cases (35). In African-Americans, it is clear that genetic variants influence bronchodilator drug responsiveness, and better understanding of the involved processes could allow for personalized therapy.

Three primary reasons may underlie the somewhat discordant results reported by different investigators. First, authors varied in their definition of "treatment-resistant asthma," have used various treatment regimens and administered different β_2-agonists to study patients, provided drugs via different routes (inhalations vs. intravenous) (2) at varied lengths of time (single, acute vs. chronic use), and per subjective physician preferences (7). Importantly, authors have also used different outcome measures and endpoints to assess drug-responsiveness. Even when using the same tool (e.g., FEV_1 change after inhaled SABA), authors have defined the drug-responsive group differently (e.g., increase by 12% from baseline, vs. increase by 15%). We have addressed this issue in the design, by inviting the original authors to look at their raw data and provide us with standardized information, to prevent misallocation of patients between the two study arms.

Second, studies have included dramatically different patient populations, in terms of sample size and enrolment rates (2,16), age, disease severity, and ethnic background. The inclusion of patients of different ethnic groups in a pharmacogenetic study can introduce significant heterogeneity due to varied allele frequencies and differing patterns of linkage disequilibrium in different populations (36), creating an unrecognized confounder in the genotype–phenotype association (37, 38). We have addressed this issue of mixed ethnic populations in the present study by obtaining ethnic background data from the original authors, when available, and analyzing individual ethnic subgroups separately before inclusion in the meta-analysis (Table 1). The study from China (11) included Han Chinese subjects, the CAMP study participants (16) were stratified by ethnicity for the present analysis, and participants in the Tucson Children's Respiratory Study (13) had both parents Hispanic or at least one white parent.

Third, some authors have suggested that the conflicting results among studies could be explained by specific combinations of polymorphisms that are commonly inherited together (β_2AR haplotypes), rather than by a single allele polymorphism (39). For example, Arg/Arg 16 was associated with a positive bronchodilator response, but the combination of homozygotes for Arg16Gln27 and heterozygotes for Arg16Gln27/Gly16Glu27 had an even greater bronchodilator response (9).

In summary, we found an association between a β_2AR polymorphism and resistance to bronchodilator drugs. Therapeutic failure of inhaled β_2-agonists in asthmatic children is associated with the Gly allele (Arg/Gly and Gly/Gly genotypes) at position 16 of the β_2-adrenergic receptor. These results suggest that genetic typing for β_2AR polymorphisms may be beneficial for children with drug-resistant asthma. However, subsequent attempts to link possible polymorphism combinations with treatment-resistance should be obtained by application of a comprehensive genome-wide approach, using a set of tagging SNPs describing common variations in β_2AR. The ability to prospectively identify children with β_2-agonist–resistant asthma is important and could potentially pave the way for alternative therapeutic pathways for high-risk patients.

Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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