Childhood asthma exacerbations and the Arg16 β_2-receptor polymorphism: A meta-analysis stratified by treatment

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Background: The Gly-to-Arg substitution at the 16 position (rs1042713) in the β_2-adrenoceptor gene *(ADRB2)* is associated with enhanced downregulation and uncoupling of β_2-receptors.
Objectives: We sought to undertake a meta-analysis to test the hypothesis that there is an interaction between the A allele of rs1042713 (Arg16 amino acid) and long-acting β-agonist (LABA) exposure for asthma exacerbations in children.
Methods: Children with diagnosed asthma were recruited in 5 populations (BREATHE, Genes-Environments and Admixture in Latino Americans II, PACMAN, the Paediatric Asthma Gene Environment Study, and the Pharmacogenetics of Adrenal Suppression with Inhaled Steroid Study). A history of recent exacerbation and asthma treatment was determined from questionnaire data. DNA was extracted, and the Gly16Arg genotype was determined.
Results: Data from 4226 children of white Northern European and Latino origin were analyzed, and the odds ratio for exacerbation increased by 1.52 (95% CI, 1.17-1.99; $P = .0021$) for each copy of the A allele among the 637 children treated with inhaled corticosteroids (ICSs) plus LABAs but not for treatment with ICSs alone (n = 1758) or ICSs plus leukotriene receptor antagonist (LTRAs; n = 354) or ICSs plus LABAs plus LTRAs (n = 569).
Conclusions: The use of a LABA but not an LTRA as an "add-on controller" is associated with increased risk of asthma exacerbation in children carrying 1 or 2 A alleles at rs1042713. Prospective genotype-stratified clinical trials are now required to explore the potential role of rs1042713 genotyping for personalized asthma therapy in children. (J Allergy Clin Immunol 2016;■■■:■■■-■■■.)

Key words: *Adrenergic receptors, asthma, child, disease exacerbation, therapeutics*

Asthma is a common condition in children in which there is heterogeneity in response to treatment with inhaled corticosteroids (ICSs), long-acting β-agonists (LABAs), and leukotriene receptor antagonists (LTRAs).[1,2] Some of this heterogeneity might reflect genetic variations within the population, and variants in the β_2-adrenoceptor gene *(ADRB2)* have been associated with increased risk for symptoms.[3-5] Of particular interest is the single nucleotide polymorphism (SNP) rs1042713, a Gly-to-Arg amino acid substitution at position 16 of the *ADRB2* gene that has been associated with differences in pulmonary function

Abbreviations used
ADRB2: β_2-Adrenoceptor gene
GALA II: Genes-Environments and Admixture in Latino Americans
HWE: Hardy-Weinberg equilibrium
ICS: Inhaled corticosteroid
LABA: Long-acting β-agonist
LTRA: Leukotriene receptor antagonist
OR: Odds ratio
PAGES: Paediatric Asthma Gene Environment Study
PASS: Pharmacogenetics of Adrenal Suppression with Inhaled Steroid Study
SABA: Short-acting β-agonist
SNP: Single nucleotide polymorphism

responsiveness to short-acting β-agonists (SABAs) in children.[6-9] The underlying mechanism of enhanced downregulation and uncoupling of β_2-receptors is thought to reflect an altered response to SABAs and LABAs.

Although the SNP rs1042713 appears to alter physiologic and clinical responses to SABAs and LABAs in pediatric populations, the clinical relevance of this association remains unclear. In 2 clinical trials there was no evidence for an association between the A allele of rs1042713 (Arg16 amino acid) and increased symptom scores.[1,7] There is inconsistent evidence from observational studies that this SNP might be relevant to exacerbations. In children the homozygous G/G genotype of rs1042713 has been linked to increased risk for hospitalization,[10] reduced bronchodilator response to SABAs,[9] prolonged stay in the hospital,[11] and intensive care unit stay[12] after presentation with acute asthma, whereas the heterozygous genotype of rs1042713 has been linked to increased risk for intubation for acute asthma.[13] Two other groups have observed associations between the A/A genotype of rs1042713 and increased exacerbations among those treated with LABAs,[3,4] but this was not confirmed in a third population.[14] These studies have also observed increased exacerbation risk[3] and poorer asthma control[4] among those children homozygous for A/A for the SNP rs1042713 receiving ICSs (but not LABAs). In one study[3] there was evidence that concomitant LTRA treatment might negate any increased risk for exacerbation associated with LABA treatment, whereas those children who are homozygous for Arg16 had better asthma outcomes when treated with LTRAs rather than LABAs in addition to ICSs.[15] Prospective studies undertaken in adult populations have found no evidence for LABA treatment being associated with adverse outcomes when added to ICS treatment.[16-18]

To better understand the interactions between the SNP rs1042713 of *ADRB2* and asthma treatment, we undertook a meta-analysis of results from 5 previously described populations.[19] Our hypothesis was that there is an interaction between the A allele of rs1042713 (Arg16 amino acid) and treatment with LABAs but not LTRAs for asthma exacerbation risk and that this risk might be further increased by exposure to daily SABAs.

METHODS

Study design

Asthmatic children were recruited to 5 cross-sectional studies (BREATHE, Genes-Environments and Admixture in Latino Americans II [GALA II], the Paediatric Asthma Gene Environment Study [PAGES], PACMAN, and PASS). The BREATHE and PAGES populations were recruited from primary and secondary care in Scotland, the PACMAN population was recruited from children attending community pharmacies in The Netherlands, GALA II recruited children in the United States and Puerto Rico who had 4 Latino grandparents, and PASS recruited children with asthma who had adrenal suppression testing in 25 hospitals across the United Kingdom. Further details of the study population's recruitment are presented in the Methods section in this article's Online Repository at www.jacionline.org. DNA was extracted from saliva or blood, and the genotypes for rs1042713 were determined. The primary outcome was asthma exacerbation (with reference to 6 months in BREATHE, PAGES, and PASS and 12 months in GALA II and PACMAN). Asthma treatment was categorized as follows: (1) as-required SABA but no preventer treatment, (2) ICS monotherapy plus as-required SABA, (3) ICS and LABA plus as required SABA, (4) ICS and LTRA plus as required SABA, and (5) ICS, LABA and LTRA plus as required SABA. As defined previously,[5] use of as required SABAs was categorized as at least once daily or less frequently. Approval was obtained from medical research ethics committees from each institute before recruitment. All participants provided verbal assent, and parents or participants provided written consent, as appropriate.

Definitions of exacerbation

For BREATHE and PAGES, the definition of exacerbation was at least 1 of the following in the previous 6 months in the context of asthma symptoms: hospital admission, course of oral steroids, or absence from school. For GALA II, an exacerbation was defined as at least 1 of the following during the previous 12 months: oral corticosteroid rescue treatment, hospitalization, or need to seek emergency asthma care. For PACMAN, an exacerbation was defined as an asthma-related visit to the emergency department, prescription of a course of oral steroids in the past 12 months, or both. The definition of exacerbation for PASS was at least 1 course of rescue oral steroids in the previous 6 months.

DNA collection, extraction, and analysis

For BREATHE, PACMAN, and PAGES, saliva was collected in commercially available pots (Oragene; DNA Genotek, Ontario, Canada), DNA was prepared with the Qiagen DNeasy 96 Kit (Qiagen, Hilden, Germany), and genotypes were determined in the Dundee laboratory by using TaqMan-based allelic discrimination assays on an ABI 7700 Sequence Detection System (Applied Biosystems, Foster City, Calif), as described previously.[3] For GALA II, DNA was extracted from whole blood, and the Axiom LAT1 array (World Array 4; Affymetrix, Santa Clara, Calif) was used to determine genome-wide genotype data, as described elsewhere.[20] For PASS, the Illumina Human OmniExpressExome-8 v1.0 chip (Illumina, San Diego, Calif) was used for genotyping.

Statistical analysis

The primary outcome was recent exacerbation, and this was related to genotype in logistic models. An additive model[3] was used (ie, a gene/dosage effect for the A allele [Arg16 amino acid]), which adjusted for confounders (ie, sex, age, and second-hand smoke exposure[3]). Each population was stratified by treatment, and risk for exacerbation per genotype was calculated in each treatment group. Daily SABA use was recorded for BREATHE, PACMAN, and PAGES, and here an interaction was sought for SABA treatment × genotype. Regression analyses in GALA II included the same covariates as in the other studies, but additionally, we included estimates of global African and Native American genetic ancestry to avoid confusion because of population stratification. Standard statistical software was used (SPSS version 22.0.0.1; SPSS, Chicago, Ill). The meta-analysis of data from the 5 populations was performed by using a fixed-effect (inverse variance–weighted) model in which the effect size estimates, β-coefficients, are weighted by their estimated SEs by using GWAMA software.[21] We estimated the power of the study to detect associations with