



Letter

β_2 -Adrenergic receptor Gly16Arg polymorphism and impaired asthma control in corticosteroid-treated asthmatic adults

β_2 -Agonists are the most commonly prescribed asthma medication, and the β_2 -adrenergic receptor gene has been studied extensively. A single-nucleotide polymorphism causing the substitution of arginine (Arg) for glycine (Gly) at position 16 (Gly16Arg) of the β_2 -adrenergic receptor affects the response to β_2 -agonists. Regular exposure to β_2 -agonists results in down-regulation and uncoupling of β_2 -adrenoreceptors with associated subsensitivity or tachyphylaxis of response.¹ Retrospective studies have reported an impaired therapeutic response in terms of peak expiratory flow in adults treated with long-acting β_2 -agonists (LABAs).² In contrast, 2 genotype-stratified randomized clinical trials with LABAs have not found a difference in peak expiratory flow response.^{3,4} In one of these studies⁴ that used methacholine challenge, Arg/Arg patients did not have an improvement in airway hyperresponsiveness when a LABA was added to an inhaled corticosteroid (ICS) compared with Gly/Gly patients. Meta-analysis of placebo-controlled trials has also revealed that Arg/Arg individuals exhibit reduced bronchoprotection to methacholine compared with Gly/Gly individuals when LABAs were added to ICSs.⁵ In asthmatic children, possession of each copy of the Arg allele was associated with a 1.74-fold increased risk of asthma exacerbations in individuals treated with an ICS plus a LABA.^{6,7} In this study, we have therefore evaluated whether the Gly16Arg polymorphism is associated with impaired asthma control in ICS-treated asthmatic adults and whether this was influenced by concomitant LABA use.

In this cross-sectional study, demographics, medication, and spirometry were recorded from patients attending a secondary care asthma clinic. As part of routine workup, the patients were also genotyped and completed the 6-point Asthma Control Questionnaire (ACQ) at the same visit. Permission to use the ACQ was obtained, and the questionnaire was not modified by the authors. In our clinic, we routinely perform Gly16Arg genotyping to help guide asthma management. As such, this audit of routine clinical care did not require internal review board approval. Caldicott guardian approval was obtained for access to the data.

The χ^2 test was used to compare categorical variables between the genotypes. The *t* test or analysis of variance was used to compare normally distributed continuous variables, whereas the Mann-Whitney or Kruskal-Wallis test was used for nonnormally distributed continuous variables. Binary logistic regression was used to calculate odds ratios for asthma that was not well controlled (ie, ACQ score >1). Statistical significance for all analyses was set at $P < .05$ (2-tailed). SPSS statistical software, version 21 (SPSS Inc, Chicago, Illinois), was used for all analyses.

A total of 223 asthmatic adults who were prescribed ICSs were included in the analysis. Most of our patients were white (99%),

and there were no individuals of African descent. The mean age was 46 years, forced expiratory volume in 1 second was 86% predicted, median ICS dose was 800 μ g/d, 73% were prescribed a LABA, and the mean ACQ score was 1.70. The frequencies of the genotypes were as follows: Gly/Gly, 47%; Arg/Gly, 40%; and Arg/Arg, 13%. No significant overall differences were found in terms of demographics, clinical characteristics, albuterol use, or ACQ between the genotypes among patients taking ICSs irrespective of concomitant LABA exposure (Table 1). Further subgroup analysis in patients taking a LABA in conjunction with an ICS comparing those possessing no copies of the Arg allele ($n = 80$) with those possessing 1 or 2 copies of the Arg allele ($n = 83$) revealed no significant differences in ACQ scores (1.82; 95% CI, 1.53–2.1; vs 1.70; 95% CI, 1.42–2.00; respectively). In such patients, albuterol use was not different between the allelic subgroups. The odds ratios for asthma that was not well controlled per Arg allele overall and among LABA users were 1.00 (95% CI, 0.68–1.48) and 0.68 (95% CI, 0.33–1.41) respectively, indicating no increased risk.

The present study found that the Gly16Arg polymorphism was not associated with impaired asthma control in ICS-treated asthmatic adults irrespective of LABA exposure. The present results are in contrast to our previous studies in children, which found an increased risk of exacerbation in relation to each copy of the Arg allele in relation to daily SABA or LABA exposure.^{6,7} Our study is in keeping with prospective genotype-stratified randomized clinical trials in adults, which have found no difference in measures of asthma control between the genotypes.^{3,4} However, measures of asthma control were not the primary outcome in these trials, and pointedly these trials were not powered to look at exacerbations. We chose to evaluate only patients with persistent asthma treated with ICSs because this is considered to be first-line controller therapy, with LABAs only being recommended as add-on therapy. In this regard, systemic and ICSs up-regulate β_2 -receptors and reverse LABA-induced tachyphylaxis *in vivo*,^{8,9} although the dose of ICS was similar between the genotypes.

One of the strengths of our study is that the participants were unselected patients taking ICSs who were attending a secondary care asthma clinic. The mean ACQ score for the patients was 1.70, indicating that these patients had inadequately controlled asthma.¹⁰ Such patients tend to be excluded from randomized clinical trials. For example, in the study by Bleecker et al, only asthmatic adults taking a SABA alone before screening were eligible for the study, indicating the study participants had essentially mild disease.³ One of the limitations of our study is that it is cross-sectional and the ACQ responses relate to the week before the clinic visit. Therefore, we were unable to assess how asthma control may vary during a longer period. In addition, we were also unable to assess treatment adherence. Another limitation is that there were only 30 Arg/Arg individuals in the study; hence, it is possible that smaller differences between the genotypes may not have been detected. In summary, we have found no evidence of impaired

Disclosures: Authors have nothing to disclose.

<http://dx.doi.org/10.1016/j.janai.2015.01.017>

1081-1206/© 2015 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved.

Table 1
Demographics and clinical characteristics for all patients taking ICSs according to β_2 -adrenergic receptor genotype

Characteristic	Gly/Gly (n = 105)	Arg/Gly (n = 88)	Arg/Arg (n = 30)	P value
Age, y	46 (43–49)	46 (43–49)	45 (39–52)	.97
Sex, M:F	45:60	39:49	9:21	.37
BMI	29.9 (28.7–31.2)	28.8 (27.3–30.4)	30.0 (27.5–33.2)	.44
FEV ₁ , % predicted	86 (82–90)	85 (81–89)	88 (82–94)	.72
FEF _{25%–75%} , % predicted	59 (53–65)	57 (51–63)	58 (49–66)	.85
FEV ₁ /FVC	0.72 (0.70–0.75)	0.71 (0.68–0.74)	0.74 (0.70–0.77)	.49
ICS dose (BDP equivalent), μ g	800 (800–1500)	800 (680–2000)	800 (400–1250)	.65
LABA, %	76	74	60	.21
LTRA, %	27	26	17	.52
ACQ-6	1.78 (1.53–2.03)	1.53 (1.28–1.78)	1.93 (1.36–2.50)	.23
Albuterol use (puffs per day)	4 (0–7)	2 (0–7)	4 (1–8)	.24

Abbreviations: ACQ-6, 6-point Asthma Control Questionnaire; BDP, beclomethasone dipropionate; BMI, body mass index; FEF_{25%–75%}, forced expiratory flow between 25% and 75% of vital capacity; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; FEV₁/FVC, forced expiratory ratio; ICS, inhaled corticosteroid, LABA, long-acting β -agonist; LTRA, leukotriene receptor antagonist.

Data are presented as means (95% confidence intervals) except for ICS dose and albuterol use, which are presented as medians (interquartile range).

control in relation to Gly16Arg polymorphism among ICS-treated adult patients with asthma.

Arvind Manoharan, MBChB*

Benjamin Griffin†

Joseph Lipworth*

Jonathan Berg, MD‡

Nicola Andrew, MSc§

Cathy Jackson, MD||

Brian Lipworth, MD*

*Scottish Centre for Respiratory Research

University of Dundee

Dundee, Scotland

†School of Medicine

University of St Andrews

Fife, Scotland

‡Clinical Genetics

University of Dundee

Dundee, Scotland

§NHS Tayside

Human Genetics Unit

Ninewells Hospital

Dundee, Scotland

||School of Medicine and Dentistry

University of Central Lancashire

Lancashire, England

b.j.lipworth@dundee.ac.uk

References

- [1] Lipworth B. β -Adrenoceptor genotype and bronchoprotective subsensitivity with long-acting beta-agonists in asthma. *Am J Respir Crit Care Med*. 2013;188:1386–1387.
- [2] Wechsler ME, Lehman E, Lazarus SC, et al. β -Adrenergic receptor polymorphisms and response to salmeterol. *Am J Respir Crit Care Med*. 2006;173:519–526.
- [3] Bleecker ER, Nelson HS, Kraft M, et al. β_2 -receptor polymorphisms in patients receiving salmeterol with or without fluticasone propionate. *Am J Respir Crit Care Med*. 2010;181:676–687.
- [4] Wechsler ME, Kunselman SJ, Chinchilli VM, et al. Effect of β_2 -adrenergic receptor polymorphism on response to longacting beta2 agonist in asthma (LARGE trial): a genotype-stratified, randomised, placebo-controlled, cross-over trial. *Lancet*. 2009;374(9703):1754–1764.
- [5] Lee DK, Currie GP, Hall IP, Lima JJ, Lipworth BJ. The arginine-16 β_2 -adrenoceptor polymorphism predisposes to bronchoprotective subsensitivity in patients treated with formoterol and salmeterol. *Br J Clin Pharmacol*. 2004;57:68–75.
- [6] Basu K, Palmer CN, Tavendale R, Lipworth BJ, Mukhopadhyay S. Adrenergic $\beta(2)$ -receptor genotype predisposes to exacerbations in steroid-treated asthmatic patients taking frequent albuterol or salmeterol. *J Allergy Clin Immunol*. 2009;124:1188–1194.
- [7] Palmer CNA, Lipworth BJ, Lee S, et al. Arginine-16 β_2 adrenoceptor genotype predisposes to exacerbations in young asthmatics taking regular salmeterol. *Thorax*. 2006;61:940–944.
- [8] Aziz I, Lipworth BJ. A bolus of inhaled budesonide rapidly reverses airway subsensitivity and β_2 -adrenoceptor down-regulation after regular inhaled formoterol. *Chest*. 1999;115:623–628.
- [9] Tan KS, Grove A, McLean A, et al. Systemic corticosteroid rapidly reverses bronchodilator subsensitivity induced by formoterol in asthmatic patients. *Am J Respir Crit Care Med*. 1997;156:28–35.
- [10] Juniper EF, Bousquet J, Abetz L, Bateman ED. Identifying 'well-controlled' and 'not well-controlled' asthma using the Asthma Control Questionnaire. *Respir Med*. 2006;100:616–621.