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# 17q21 variant increases the risk of exacerbations in asthmatic children despite inhaled corticosteroids use

To the Editor,

Approximately 25% of the asthmatic children suffer from uncontrolled asthma despite regular use of inhaled corticosteroids (ICS).<sup>1</sup> Variation within the 17q21 locus is the strongest genetic determinant for childhood-onset asthma.<sup>2</sup> Recently, the influence of this locus on treatment outcomes has been shown in several studies.<sup>3-4</sup> The Pharmacogenomics in Childhood Asthma (PiCA) consortium is a multiethnic consortium that brings together data from  $\geq 14\ 000$  asthmatic children/young adults from 12 different countries to study the pharmacogenomics of uncontrolled asthma despite treatment.<sup>5</sup> In 14 PiCA populations (with over 4000 asthmatic patients), we studied the association between variation in the 17q21 locus, and asthma exacerbations despite ICS use. We specifically focused on rs7216389, a single nucleotide polymorphism (SNP) in the 17q21 locus strongly associated with childhood asthma and initially identified by Moffatt et al.<sup>2</sup>

Ten PiCA studies included patients with non-Hispanic European origins, two included Hispanic patients, one African American, and one included East Asian patients. Additional details of the study populations can be found in the Data S1. Two outcomes were assessed: (i) asthma-related hospitalizations/emergency department visit (ED) visits and (ii) short courses of oral corticosteroid (OCS) use reported by the parent/child at the study visit or based on completed study questionnaires. Age, gender, genotype data, and exacerbation data were available for 4529 steroid-treated children and young adults (Table 1). Logistic regression analysis was used to assess the risk of exacerbations when carrying rs7216389. Due to potential heterogeneity between cohorts, the odds ratios (ORs) were meta-analyzed with the inverse variance weighting method assuming random effects. See Data S1 for more detail.

The risk allele (T) frequency was highest in East Asians ( $n = 182$ ,  $T = 0.81$ ), followed with African Americans ( $T = 0.79$ ,  $n = 468$ ) and Hispanics ( $T = 0.66$ , total  $n = 916$ ), and it was less frequent in patients with European ancestry (ranged between 0.54 and 0.62, total  $n = 2963$ ). The genotype distribution of the SNP was in Hardy-Weinberg equilibrium in all cohorts. There was a low to moderate heterogeneity between studies (Figure 1). Exacerbation rates ranged between 6.5% (PACMAN) and 77.2% (HPR) for OCS use and 6% (PACMAN) and 58% (GALA II and HPR) for hospitalizations/ED visits.

Thirty percent (1378 out of 4454) of the patients reported hospitalizations/ED visits. In the meta-analysis of 13 studies, rs7216389 was statistically significantly associated with asthma-related ED visits/hospitalizations, (summary OR per increase in risk allele: 1.32, 95% CI: 1.17- 1.49,  $P < .0001$ ,  $I^2 = 3.9\%$ ) (Figure 1A). In a subgroup analysis, the effect estimates for hospitalizations/ED visits were approximately the same for both non-Hispanic whites ( $n = 2888$ , OR: 1.33, 95% CI: 1.10-1.61,  $P = .004$ ,  $I^2 = 30.2\%$ ) and Hispanics ( $n = 916$ , OR: 1.31, 95% CI: 1.06-1.63,  $P = .01$ ,  $I^2 = 0.00\%$ ). Thirty-one percent (1269 out of 4050) of the patients reported OCS use/high-dose ICS. In the meta-analysis of the nine studies, the rs7216389-T was statistically significantly associated with an increased risk of OCS use/high-dose ICS (summary OR per increase in variant allele: 1.19, 95% CI: 1.04-1.36,  $P = .01$ ,  $I^2 = 22.8\%$ ) (Figure 1B). Rs7216389 was associated with OCS use in the meta-analysis of seven European studies ( $n = 2492$ , OR: 1.26, 95% CI: 1.09-1.45,  $P = .002$ ,  $I^2 = 6.2\%$ ) but not in Hispanics ( $n = 916$ , OR: 0.96, 95% CI: 0.76-1.22,  $P = .7$ ,  $I^2 = 0.00\%$ ). Differences in the minor allele frequencies and LD structures among different ethnicities can influence results of the association studies.<sup>6</sup> This could be one of the potential explanations why we did not find a significant association in African Americans and patients from Singapore.

A sensitivity analysis was performed to investigate this association in children  $\geq 5$  years of age. When excluding children  $< 5$  years of age in the meta-analysis, the results remained significant. In the meta-analysis of 13 studies, the SNP was associated with asthma-related hospitalization/ED visits ( $n = 4254$ , OR: 1.32, 95% CI: 1.18-1.49,  $P < .0001$ ,  $I^2 = 0.0\%$ ) (Figure S1). Regarding OCS use, 10 studies collected data on patients  $\geq 5$  years of age ( $n = 3771$ ). In the meta-analysis of 10 studies, rs7216389 was associated with the OCS use (summary OR: 1.20, 95% CI: 1.05-1.38,  $P = .01$ ,  $I^2 = 21.7\%$ ) (Figure S2).

We also performed a meta-analysis of the studies that had sufficient data available on preschool children (2-4 years of age). Although the effect estimates in younger children were in the same direction for both outcomes, the results were not statistically significant (Figures S3 & S4). All preschool studies solely included European children.

Altered expression of *ORMDL3* and *GSDMB* by 17q21 locus variants may play a key role in childhood asthma onset.<sup>2,7</sup> Two 17q21 asthma-risk variants (rs4065275 and rs12936231) in high

Farzan and Vijverberg equally contributed to this study.

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**TABLE 1** Characteristics of the study populations

	BAMSE <sup>a</sup> (n = 122)	BREATHE (n = 808)	CAMP <sup>a</sup> (n = 172)	COPISAC2000 <sup>a,b</sup> (n = 54)	ESTATe (n = 95)	followMAGICS <sup>a</sup> (n = 150)	GALA II <sup>a</sup> (n = 744)	HPR <sup>a</sup> (n = 172)	PACMAN (n = 665)	PAGES (n = 308)	PASS <sup>a</sup> (n = 390)	SAGE II <sup>a</sup> (n = 468)	SCSGES <sup>a</sup> (182)	Slovenia <sup>a</sup> (n = 199)
Patient characteristic														
Age (y), mean (SD)	8.37 (0.41)	9.8 (4.0)	8.8 (2.1)	3.3 (1.0)	10.8 (4.3)	17.13 (3.03)	12.1 (3.2)	9.8 (2.7)	8.7 (2.3)	9.2 (3.8)	11.1 (4.0)	13.5 (3.4)	13.35 (5.09)	10.9 (3.41)
Male gender, % (n)	79 (96)	60.8 (491)	55.2 (95)	54 (29)	57.9 (55)	59.3 (89)	56.8 (423)	49.4 (85)	61.1 (406)	56.8 (175)	55.9 (218)	54.1 (253)	67.6 (123)	54.8 (109)
Asthma exacerbations in past year														
Asthma-related ED visit/hospital admission, % (n) <sup>a</sup>	14.7 (18)	19.0 (154)	13.4 (23)	–	10.5 (10)	8.6 (13)	58.3 (434)	58.1 (100)	6.0 (39/644)	15.6 (48)	76 (296)	44.7 (209)	20.3 (37)	35.6 (71)
Oral corticosteroid use, % (n)	–	31.7 (256)	47.1 (81)	11.1 <sup>b</sup> (6)	36.8 (35)	–	42.3 (315)	77.3 (133)	6.5 (43)	43.2 (133)	52 (203)	29.3 (137)	20.3 (37)	–
BTS treatment step														
2, %	–	65.6	<sup>c</sup>	–	60	28.7	41.1	60.7	72	25.6	–	68.6	–	–
3, %	–	18.4	–	–	37.9	60.7	43.6	36.4	22.3	61	–	25	–	–
4, %	–	16.0	–	–	2.1	10.6	15.3	2.9	5.7	13.3	–	6.4	–	–
Rs7216389														
T-allele frequency	0.57	0.56	0.58	0.62	0.60	0.58	0.66	0.66	0.59	0.58	0.60	0.79	0.81	0.54

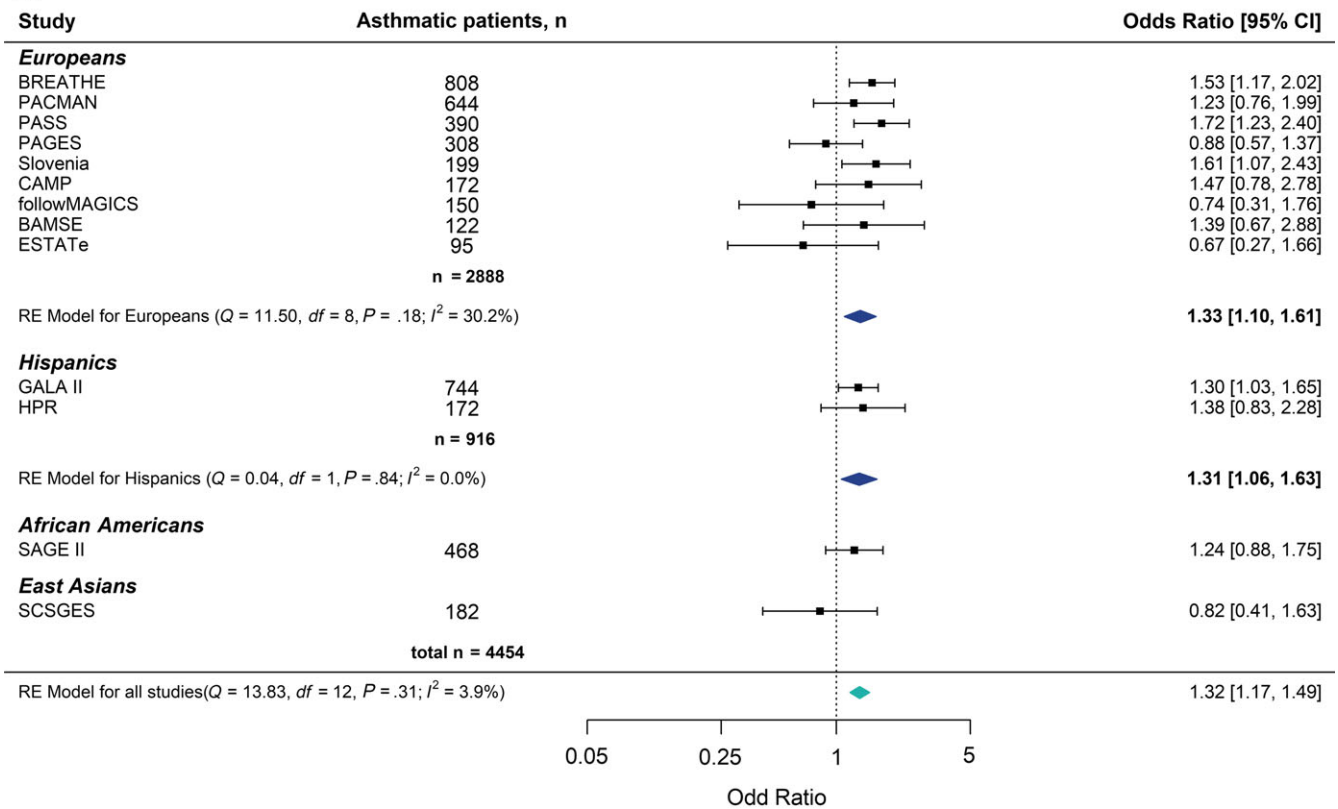
–, data not available; BTS, British Thoracic Society; ED, emergency department; SD, standard deviation; y, years.

<sup>a</sup>DNA was extracted from peripheral blood samples in these studies, and in the remaining, DNA was extracted from saliva samples.

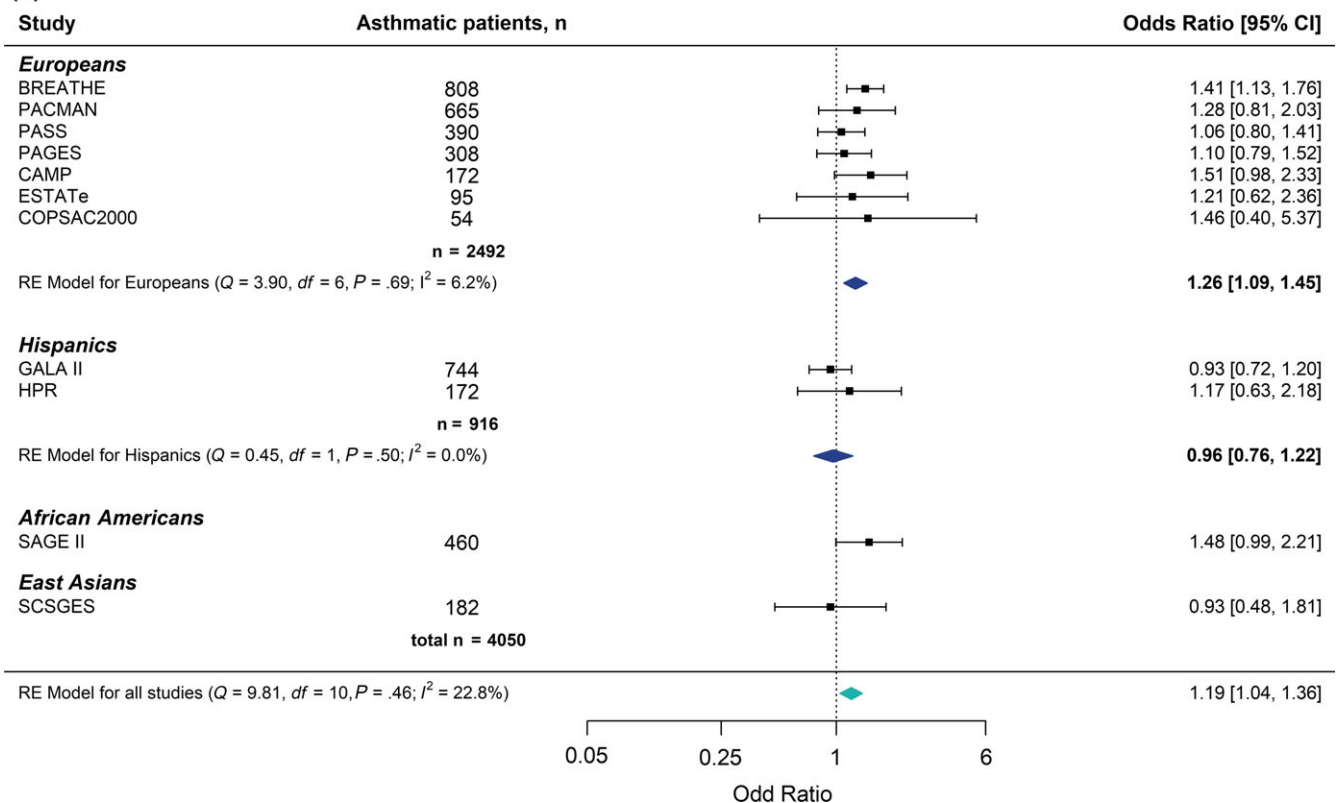
<sup>b</sup>Patients with exacerbations were treated with oral corticosteroid or high-dose inhaled corticosteroids.

<sup>c</sup>CAMP is randomized clinical trial of mild to moderate asthmatics, and all children were on 200 µg of budesonide (ICS) plus SABA as needed.

(A)



(B)



**Figure 1.** Forest Plots of rs7216389 for (A) asthma-related hospitalizations/ED visits in thirteen studies and (B) OCS/high-dose ICS use in eleven studies. Odds Ratios (OR) and corresponding 95% Confidence Intervals (95% CI) for individuals with rs7216389, controlling for age, gender, and BTS treatment step [Colour figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

linkage disequilibrium (LD) with rs7216389 were reported to switch CTCF-binding sites that resulted in increased expression of ORMDL3 in CD4+ T cells which subsequently reduced interleukin-2 production.<sup>8</sup>

Rs7216389 has previously shown to be associated with exacerbations<sup>3</sup> and poor lung function in Caucasian children using ICS.<sup>4</sup> Even though in our study Caucasians were the largest group, this study is the largest multiethnic population evaluating the association between 17q21 variant and asthma exacerbations in ICS users. Rs7216389 seems to increase bronchial responsiveness and therefore exacerbation rates in children,<sup>9</sup> suggesting that carriers of rs7216389 might have a more severe form of asthma. However, by adding British Thoracic Society (BTS) treatment steps as a marker of disease severity to the model, we argue that the association reflects, at least partly, poor response to ICS.

Limitations of the study include the use of retrospective reporting of exacerbations in the observational cohort studies. However, the effect was also observed in a clinical trial population (CAMP), where exacerbations were reported prospectively. Hence, we do not believe that using retrospective data has significantly influenced the results. As not all studies had data available on both hospitalizations/ED visits and OCS use, we did not combine the two outcomes in our analysis. Furthermore, as information on treatment adherence was not available in all included studies, it was not considered in the analysis.

We show that 17q21, a widely replicated asthma susceptibility locus, is also associated with an increased risk of exacerbations in children/young adults treated with ICS. A better understanding of the molecular mechanisms underlying exacerbation-prone phenotype of pediatric asthma could lead to a better classification of different pediatric asthma phenotypes and the identification of novel treatment targets.














## CONFLICTS OF INTEREST

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#### SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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## Association of mast cells with clinical, endoscopic, and histologic findings in adults with eosinophilic esophagitis

To the Editor,

Eosinophilic esophagitis (EoE) presents with diverse features which can differ between children and adults, as well as among adults, but eosinophils alone do not account for this heterogeneity.<sup>1,2</sup> Mast cells are involved in EoE pathogenesis, are highly increased in EoE compared to non-EoE controls, and mast cell-associated genes are upregulated in EoE.<sup>2-5</sup> Mast cells also produce the profibrotic factor TGF- $\beta$ 1 and promote smooth muscle contraction.<sup>6</sup> However, the extent to which mast cell presence correlates with

clinical features of EoE is unknown. We aimed to determine whether esophageal mast cell levels correlated with clinical symptoms, endoscopic findings, and histologic features in newly diagnosed adults with EoE.

We performed a secondary analysis of data and biospecimens collected during a prospective cohort study of EoE cases, details of which have been previously described.<sup>7</sup> The parent study included adults (>18) undergoing outpatient endoscopy for symptoms of esophageal dysfunction. EoE was diagnosed by consensus guidelines.<sup>8</sup>

**TABLE 1** Patient characteristic, and characteristics stratified by the highest and lowest mast cell quartile, and by mast cell to eosinophil ratios  $\leq 1$  and  $> 1$

Characteristic	Overall EoE population (n = 96)	Lowest mast cell quartile (n = 24)	Highest mast cell quartile (n = 24)	P	Mast cell to eos ratio $\leq 1$ (n = 72)	Mast cell to eos ratio $> 1$ (n = 24)	P
Mast cell density (mean cells/mm <sup>2</sup> $\pm$ SD)	266.8 $\pm$ 180.0	88.7 $\pm$ 32.6	515.3 $\pm$ 157.4	-	235.1 $\pm$ 142.2	361.6 $\pm$ 242.6	0.002
Eosinophil density (eos/mm <sup>2</sup> ; mean $\pm$ SD)	555.9 $\pm$ 478.1	304.2 $\pm$ 212.0	717.5 $\pm$ 501.1	<0.001	664.6 $\pm$ 498.8	229.8 $\pm$ 168.8	<0.001
Age at diagnosis (mean $\pm$ SD)	37.2 $\pm$ 12.7	38.0 $\pm$ 14.2	38.4 $\pm$ 13.6	0.91	37.1 $\pm$ 12.6	37.6 $\pm$ 13.2	0.88
Male (n, %)	54 (56)	10 (42)	15 (63)	0.15	38 (53)	16 (67)	0.24
White (n, %)	91 (95)	23 (96)	24 (100)	0.31	68 (94)	23 (96)	0.79
Symptoms							
Dysphagia (n, %)	94 (98)	24 (100)	23 (96)	0.31	71 (99)	23 (96)	0.41
>5 y of dysphagia (n, %)	53 (60)	13 (56)	12 (55)	0.51	37 (57)	16 (70)	0.67
VAS <sup>a</sup> score (mean $\pm$ SD)	3.5 $\pm$ 2.7	2.4 $\pm$ 1.9	3.6 $\pm$ 2.8	0.12	3.5 $\pm$ 2.6	3.5 $\pm$ 3.0	0.97
Heartburn (n, %)	8 (8)	1 (4)	2 (8)	0.55	7 (10)	1 (4)	0.39

(Continues)