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Original Article

ORMDL3/GSDMB genotype as a risk factor for early-onset adult asthma is linked to total serum IgE levels but not to allergic sensitization

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Abbreviations:

ORMDL3	orosomucoid-like 3
GSDMB	gasdermin B
GWAS	genome-wide association study
SNP	single-nucleotide polymorphism
ICAM1	intercellular adhesion molecule 1

ABSTRACT

Background: An orosomucoid-like 3 (*ORMDL3*)/gasdermin B (*GSDMB*) gene locus on chromosome 17q is consistently associated with childhood-onset asthma, which is highly atopic. As some evidence suggests the relationship between asthma and allergic sensitization reflects asthma patient susceptibility to augmented IgE responses driven by common environmental allergens rather than an increased asthma risk after allergen exposure, we aimed to determine any relationships between this locus region and childhood-onset adult asthma with regard to serum total IgE levels or allergic sensitization.
Methods: We conducted a case–control association study using three independent Japanese populations (3869 total adults) and analyzed the ORs for association of rs7216389, an expression quantitative trait locus for *ORMDL3/GSDMB*, with adult asthma according to onset age. Additionally, associations between the rs7216389 genotype and total serum IgE levels or allergic sensitization was examined.
Results: Rs7216389 was associated with both childhood-onset adult asthma (OR for asthmatic patients afflicted at the age of 10 years or younger = 1.61, $p = 0.00021$) and asthmatic patients with higher levels of total serum IgE (OR for asthmatic patients with IgE ≥1000IU/mL = 1.55, $p = 0.0033$). In both healthy controls and in the combined healthy and asthmatic individuals, rs7216389 was correlated with increased total serum IgE levels ($p < 0.0005$), but not allergic sensitization ($p > 0.1$).
Conclusions: ORMDL3/GSDMB is an important susceptibility gene for childhood-onset adult asthma in Japanese populations and this association is linked to elevated total serum IgE levels but not to allergic sensitization.

Introduction

Excessive, IgE-mediated immune responsiveness to common airborne allergens is believed to be an important causative factor for asthma. Nevertheless, as there is surprisingly little overlap between genes affecting IgE levels and those mediating asthma susceptibility, allergic sensitization is sometimes thought to be secondary to asthma and not a primary driver of the disease.[1] In this respect, using a Mendelian randomization strategy, we previously examined whether allergic sensitization is a cause of asthma and found that the estimated proportion of atopic asthma cases attributable to genetic susceptibility to allergic sensitization was 16.6%. This supports the contention that the relationship between asthma and sensitization to common allergens reflects the susceptibility of asthma patients to augmented IgE responses driven by common environmental allergens rather than an increased asthma risk after allergen exposure.[2]

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To obtain further insights into the causality of allergic sensitization in the pathogenesis of atopic asthma, we focused on the genetic effect of orosomucoid-like 3 (*ORMDL3*)/gasdermin B (*GSDMB*), which is consistently observed in childhood-onset asthma, most of which is atopic. However, any associations between this genetic region and total serum IgE levels, allergic sensitization or allergic rhinitis are inconsistent.[1,3–5] A pioneering study by Moffatt *et al.* showed that multiple markers at the 17q21 locus have a strong association with childhood-onset asthma and that rs7216389 was the most strongly associated marker,[6] while a Japanese study previously confirmed the association of rs7216389 with childhood atopic asthma.[7] Chromosome 17q21 contains several genes linked to asthma in Genome-wide association studies (GWASs), including *ORMDL3* and *GSDMB*. Although its physiological functions are not well understood, *ORMDL3* has been reported to contribute to airway remodeling and inflammation by selectively activating the unfolded protein response in the endoplasmic reticulum[3,8] and altering Ca^{2+} flux.[9] *GSDMB* has been reported to be expressed in ciliated airway epithelial cells and induce inflammatory caspase-mediated pyroptotic cell death.[10]

Meanwhile, a previous general population study examined the association of asthma or allergic rhinitis with total serum IgE levels and skin-test reactivity to allergens in 2657 participants,[11] showing that asthma prevalence was related to total serum IgE levels regardless of the atopic status. This suggests that exaggerated IgE production in a noncognate manner rather than allergen-specific manner may be primarily involved in asthma pathogenesis. A genetic study in Amish families revealed evidence for linkage of the chromosome 5q31.1 region, especially to the *IL4* gene, to total serum IgE levels but not with allergen-specific IgE levels, indicating that interleukin-4 (IL-4) or a nearby gene in 5q31.1 regulates IgE production in a nonantigen-specific fashion.[12] Therefore, overexpression of *ORMDL3*/*GSDMB* could also contribute to the development of asthma through exaggerated, noncognate rather than cognate IgE responses. Clarifying the relationship of this locus with total serum IgE levels and allergic sensitization may help to reveal the immunological mechanisms of how this locus is involved in asthma pathogenesis.

We thus initially conducted a candidate gene case–control approach to reveal the genetic contribution of rs7216389 to adult asthma in Japanese patients, specifically focusing on age at asthma onset. Then, we examined if the relationship between this single-nucleotide polymorphism (SNP) and early-onset asthma is linked to increased levels of total serum IgE or the presence of IgE sensitization to common inhaled allergens.

Methods

Study participants

We studied independent 3 adult Japanese populations. The first population (Tsukuba Cohort 1) included 967 healthy adult volunteers without respiratory diseases and 242 adult asthmatic patients. All participants in this cohort had genome-wide SNP typing.[13] The second population (Tsukuba Cohort 2) included 513 healthy adult volunteers and 605 asthmatic patients.[14,15] In these 2 populations, the healthy adult volunteers were recruited from individuals who underwent an annual medical checkup at the Tsukuba Medical Center while asthmatic patients were recruited from the University of Tsukuba Hospital and its affiliated hospitals. The third population (Hokkaido Cohort) included 929 healthy adult volunteers and 613 asthmatic patients recruited from the Hokkaido University Hospital and its affiliated hospitals.[14–16]

A clinical diagnosis of asthma was based on the presence of recurrent episodes of 2 or more of the 3 symptoms (coughing, wheezing, and dyspnea) associated with demonstrable reversible airflow limitation and/or increased airway hyperresponsiveness to a bronchoconstrictor.[17] The data for age at asthma onset were self-reported but to evaluate the onset age as accurately as possible, patients were asked about episodes of coughing, wheezing, or dyspnea during childhood and adolescence.[18] Healthy adults in all populations had no diagnostic histories of pulmonary diseases such as asthma or COPD. The multiple allergen simultaneous test-26 chemiluminescent assay was used to quantify levels of specific serum IgE antibodies. We defined the presence of allergic sensitization as a positive response to at least one of 14 common, inhaled allergens, including *Dermatophagoides farinae*, house dust, timothy grass, sweet vernal grass, ragweed mixture, mugwort, Japanese cedar, cat epithelium, dog epithelium, *Penicillium*, *Cladosporium*, *Candida*, *Alternaria*, and *Aspergillus*.[15]

Ethics statement

This study was approved by the Human Genome Analysis and Epidemiology Research Ethics Committee of the University of Tsukuba (Ethical approval number: H29-294) and by the Human Genome/Gene Analysis Research Ethics Review Committees of the Tsukuba Medical Center, RIKEN, and the Hokkaido University School of Medicine. Written, informed consent was obtained from each participant before the study, which was performed in accordance with the principles of the Declaration of Helsinki. Patient anonymity was preserved using methods approved by the Ethics Committee.

Genotyping

We primarily focused on rs7216389, one of the strongest markers associated with childhood asthma in Japanese and non-Japanese populations[6,7]; the T allele at rs7216389 is consistently correlated with increased *ORMDL3* and *GSDMB* mRNA expression.[5,19] Genomic DNA was extracted from peripheral blood samples by an automated DNA extraction system (QuickGene-610L; Fujifilm, Tokyo, Japan). In Tsukuba Cohort 1, 967 healthy controls and 242 asthmatic patients underwent GWAS genotyping using Illumina HumanHap 550k v3/610-Quad BeadChips (Illumina, San Diego, CA, USA).[13] For individuals without GWAS genotyping (Tsukuba Cohort 2 and Hokkaido cohort), genotypes for rs7216389 were carried out using the TaqMan allele-specific amplification method (Applied Biosystems, Foster City, CA, USA).

Statistical analysis

The genotype at the rs7216389 was examined for association with asthma via logistic regression modeling (crude model) and by adjusting for potential confounding factors including age, gender, and smoking status (never, ex, or current). Combined results from three independent populations were analyzed by adjusting for the cohort in the logistic regression model before plotting ORs for associations between rs7216389 and onset age-specific subsets of asthma as well as associations between rs7216389 and specific subsets of asthma according to total serum IgE.

The genotype at the rs7216389 was examined for associations with allergic sensitization using logistic regression modeling adjusted for age, gender, smoking status, and total serum IgE levels (log-transformed). General linear models were used to assess any associations between rs7216389 genotype and total serum IgE levels (log-transformed) after adjusting for age, gender, smoking status and/or allergic sensitization.[13,20,21] These analyses were done both in non-asthmatic healthy individuals only and in the combined healthy individuals and asthmatic patients. Analyses

conducted on data from the combined healthy individuals and asthmatic patients were also adjusted for the presence of asthma. The cohort was again included in the model as an additional covariate when we analyzed the combined results from three cohorts in a general linear model. All analyses were conducted with SPSS (version 25) and *P* values of <0.05 were considered statistically significant.

Hardy–Weinberg equilibrium was confirmed for the genotype frequencies in healthy individuals of the three cohorts. To measure the effect of population heterogeneity, we calculated the I^2 heterogeneity index using *PLINK* ver. 1.07.

Results

The characteristics of the Tsukuba Cohort 1, Tsukuba Cohort 2 and Hokkaido Cohort are provided in Table 1. Genotypes at the rs7216389 in the non-asthmatic control groups of the three cohorts did not deviate from Hardy–Weinberg equilibrium ($P > 0.05$).

The combined meta-analysis of the three independent cohorts showed that greater numbers of the T allele at rs7216389 were found in early-onset adult asthmatic patients afflicted at the age of 10 years or younger (adjusted OR = 1.61; adjusted $P = 0.00021$) (Table 2). Compared to older-onset adult asthma patients (age at onset > 10 years old), those patients with early-onset adult asthma were characterized by the presence of allergic sensitization ($P < 1.0 \times 10^{-10}$; Pearson's chi-square tests) and increased levels of total serum IgE (log-transformed) ($P < 1.0 \times 10^{-10}$; two-tailed student's *t*-tests). The association between levels of total serum IgE and early-onset asthma remained strong even after adjusting for the confounding effect of atopic dermatitis in two Tsukuba cohorts (Supplementary Table 1). The OR for association between rs7216389 and onset age-specific subsets of asthma showed that the OR gradually increased as the cut-off for the onset age became younger (Fig. 1A). This analysis clearly indicates that the genetic contribution of rs7216389 becomes increasingly greater as the age at asthma onset becomes younger. Furthermore, the association between the T allele at rs7216389 and asthma was greater when total serum IgE levels were higher regardless of asthma onset age (Table 2, Fig. 1B).

In healthy controls, while rs7216389 was not related to allergic sensitization (OR = 0.90, p = 0.15) (Table 3), the T allele at rs7216389 was associated with increased total serum IgE levels (log-transformed) (p = 0.00033) (Table 4A). This association became even stronger when we added allergic sensitization as an additional covariate (p = 0.000063) (Table 4B). In addition, when the presence of allergic rhinitis and/or atopic dermatitis was adjusted in the statistical models, we did not see any changes in these results (Supplementary Table 2, 3).

In the whole population, including healthy controls and asthmatic patients (3475 total adults with total serum IgE and other confounding factor data), rs7216389 was again associated with increased total serum IgE levels (log-transformed) (p = 0.000017) but not with allergic sensitization (OR = 0.91, p = 0.14) (Table 5, 6). Excluding cedar pollen-specific IgE responsiveness from the definition of allergic sensitization did not significantly affect these results. I^2 was 0 for both early-onset asthma (p for Cochrane's Q statistic = 0.89) and asthma with increased levels of total serum IgE (0.45), revealing no obvious population heterogeneity (Table 2).

Discussion

In the present study, our combined analysis of the three independent Japanese cohorts revealed a significant association of rs7216389 with highly atopic early-onset adult asthma but not with allergic sensitization *per se*, and revealed that the rs7216389 allele was associated with total serum IgE levels independently of the presence of asthma and allergic sensitization. These findings suggested that this SNP could plausibly be associated with early-onset adult asthma to the extent that total IgE but not allergic sensitization causally contributes to the pathogenesis of the early-onset disease phenotype. In Singaporean adults of Chinese ancestry, functional variants of 17q12-21 were also associated with allergic asthma but not allergic rhinitis. Results of this study were also consistent with our findings in that this region showed stronger associations with higher levels of total serum IgE compared with the association observed for the HDM-specific IgE titers in non-asthmatic healthy volunteers,[4] suggestive of primary *ORMDL3/GSDMB* region involvement in non-cognate IgE production.

Table 1
Characteristics of the study populations.

	Tsukuba Cohort 1		Tsukuba Cohort 2		Hokkaido replication Cohort	
	Healthy controls	Asthmatic patients	Healthy Controls	Asthmatic patients	Healthy controls	Asthmatic patients
Number of participants	967	242	513	605	929	613
Sex (female, %)	526 (54.4)	143 (59.1)	264 (51.5)	348 (57.5)	382 (41.1)	349 (56.9)
Age, y (range)	50.0 (27–74)	51.2 (20–75)	51.2 (22–81)	59.3 (18–100)	45.6 (18–84)	51.9 (18–84)
Age of asthma onset (range)		37.5 (0–70)		42.0 (1–88)		37.1 (0–80)
Smoking status (%)						
Never smoker	607 (62.8)	196 (81.3)	309 (60.2)	333 (57.9)	485 (57.0)	342 (56.3)
Ex-smoker	199 (20.6)	14 (5.8)	149 (29.0)	184 (32.0)	127 (14.9)	174 (28.7)
Current smoker	161 (16.6)	31 (12.9)	55 (10.7)	58 (10.1)	239 (28.1)	91 (15.0)
allergic sensitization (%)	541 (55.9)	157 (73.0)	327 (63.7)	270 (73.2)	487 (52.5)	413 (68.4)
atopic dermatitis	0 (0.0)	26(10.8)	53(10.3)	32(5.3)	NA	NA
allergic rhinitis	358 (37.0)	70 (34.8)	206 (40.2)	44 (21.2)	NA	NA
FEV_1/FVC (%, SD)	83.2 (5.2)	74.9 (11.1)	81.8 (7.1)	69.3 (12.7)	82.8 (7.5)	68.4 (13.2)
Total IgE (log, SD)	1.73 (0.56)	2.22 (0.61)	1.92 (0.62)	2.24 (0.65)	1.82 (0.62)	2.28 (0.67)

IgE, immunoglobulin E; NA, not available; SD, standard deviation.
In asthmatic patients in the Tsukuba cohort 1, information on smoking, allergic sensitization, atopic dermatitis, allergic rhinitis, FEV_1/FVC, and serum IgE was missing in 1, 27, 1, 41, 5, and 20 individuals, respectively. In healthy controls in the Tsukuba cohort 2, information on FEV_1/FVC was missing in 8 individuals. In asthmatic patients in the Tsukuba cohort 2, information on asthma onset age, smoking, allergic sensitization, allergic rhinitis, FEV_1/FVC, and serum IgE was missing in 32, 30, 236, 397, 65, and 152 individuals, respectively. In healthy controls in the Hokkaido cohort, information on smoking, allergic sensitization, FEV_1/FVC, and serum IgE was missing in 78, 2, 91, and 4 individuals, respectively. In asthmatic patients in the Hokkaido cohort, information on asthma onset age, smoking, allergic sensitization, FEV_1/FVC, and serum IgE was missing in 23, 6, 9, 36, and 10 individuals, respectively.

Table 2
Results of association analysis in 3 populations and meta-analysis for rs7216389.

	Tsukuba Cohort 1				Tsukuba Cohort 2				Hokkaido Cohort				Meta-analysis[‡]	
	n	RAF (T)	OR (95% CI)	*P* value	n	RAF (T)	OR (95% CI)	*P* value	n	RAF (T)	OR (95% CI)	*P* value	OR (95% CI)	*P* value
1) crude model														
Healthy controls	967	0.72			513	0.74			929	0.74				
Patients with early-onset asthma (onset at ≤10 years)	49	0.80	1.57 (0.95–2.62)	0.081	89	0.81	1.51 (1.01–2.27)	0.045	98	0.82	1.58 (1.10–2.28)	0.014	1.57 (1.24–1.99)	0.00021
Patients with higher total IgE (IgE ≥ 1000 IU/ml)	21	0.86	2.44 (1.01–5.88)	0.047	54	0.79	1.32 (0.81–2.15)	0.27	79	0.82	1.59 (1.06–2.38)	0.025	1.58 (1.18–2.11)	0.0021
2) adjusted model[†]														
Healthy controls	967	0.72			513	0.74			851	0.74				
Patients with early-onset asthma (onset at ≤10 years)	48	0.79	1.40 (0.81–2.42)	0.23	87	0.81	1.55 (1.01–2.38)	0.047	96	0.83	1.65 (1.11–2.44)	0.012	1.61 (1.25–2.06)	0.00021
Patients with higher total IgE (IgE ≥ 1000 IU/ml)	21	0.86	2.44 (1.01–5.88)	0.047	51	0.77	1.28 (0.77–2.12)	0.34	78	0.83	1.61 (1.06–2.43)	0.024	1.55 (1.16–2.09)	0.0033

RAF, risk allele frequency; OR, Odds ratio; CI, Confidence interval; IgE, Immunoglobulin E.
[†] The model was adjusted for age, gender, and smoking status.
[‡] *I2* was 0 in the meta-analysis for early-onset asthma (p for Cochrane's Q statistic = 0.89) or for asthma with increased levels of total serum IgE (0.45).

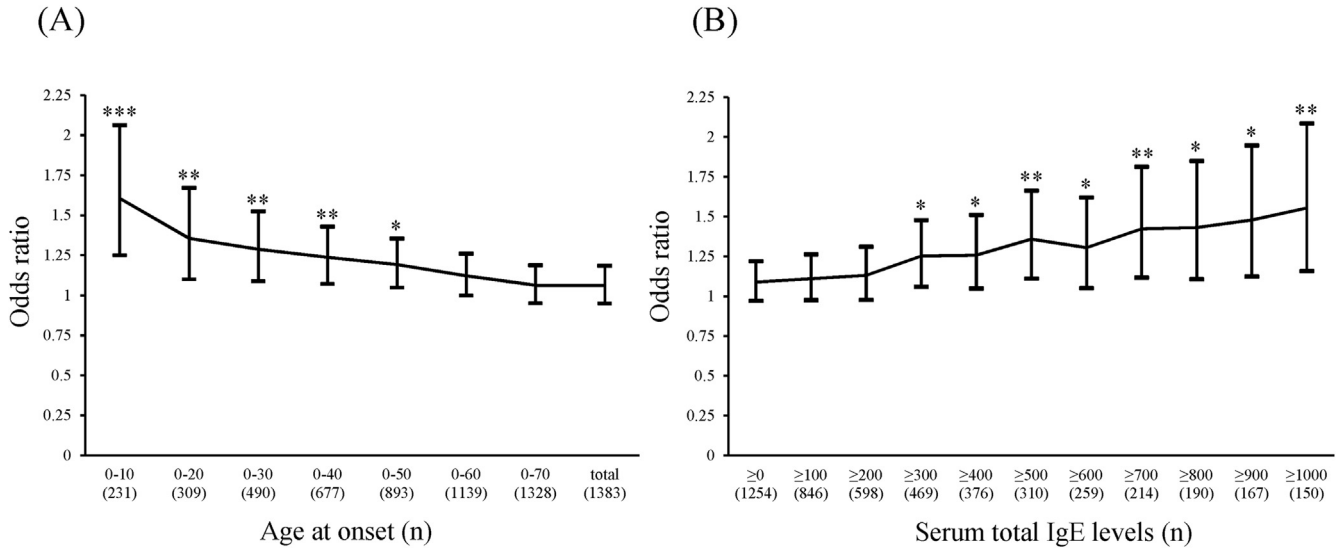

Fig. 1. (A) ORs for association between rs7216389 and age of onset-specific subsets of asthma in 1383 asthmatic patients and 2331 healthy controls from 3 independent Japanese populations. The OR (95% CI) as adjusted by age, gender, smoking status, and the cohorts was plotted with regard to rs7216389 and age at onset of specific subsets of asthma. ORs are highlighted if they are significantly greater than 1 (*p < 0.05, **p < 0.005, ***p < 0.0005). **(B)** ORs for association between rs7216389 and asthma according to total serum IgE in 1254 asthmatic patients and 2331 healthy controls from 3 independent Japanese populations. The OR (95% CI) as adjusted by age, gender, smoking status, and the cohorts was plotted with regard to rs7216389 and specific subsets of asthma according to total serum IgE levels. ORs are highlighted if they are significantly greater than 1 (*p < 0.05, **p < 0.005).

Table 3
Association between rs7216389 and the allergic sensitization in healthy controls.

Genotype	Tsukuba Cohort 1			Tsukuba Cohort 2			Hokkaido Cohort			Meta-analysis		
	Atopy (%)	OR (95% CI)	*P* value	Atopy (%)	OR (95% CI)	*P* value	Atopy (%)	OR (95% CI)	*P* value	Atopy (%)	OR (95% CI)	*P* value
CC	47 (65.3)	0.78	0.037	23 (71.9)	0.92	0.65	30 (41.1)	1.04	0.78	100 (56.5)	0.90	0.15
CT	225 (55.4)	(0.62–0.99)		121 (59.3)	(0.65–1.31)		158 (53.0)	(0.81–1.32)		504 (55.5)	(0.77–1.04)	
TT	269 (55.0)			183 (66.1)			254 (53.2)			706 (56.8)		

OR, Odds ratio; CI, Confidence interval.
The analysis was adjusted for age, gender, smoking status, and total serum IgE (log-transformed).

Children with the risk genotype (TT) at rs7216389 who had had rhinovirus-induced wheezing within 3 years after birth saw increases in asthma prevalence later in childhood compared to children who did not wheeze.[22] In fact, *ORMDL3* was reported to be involved in susceptibility to rhinoviral infection by regulating the transcription and protein expression of the major receptor for human rhinovirus, intercellular adhesion molecule 1 (ICAM1).[23] In addition to viral infection, early tobacco smoke exposure also enhances risk caused by the 17q21 region on the development of asthma.[24] Higher levels of total IgE was found in smokers regardless of skin reactivity to common inhaled allergens.[25] Both rhinovirus infection and tobacco smoke exposure induce thymic stromal

Table 4
Association between rs7216389 and total serum IgE (log-transformed) in healthy controls.

Genotype	Tsukuba Cohort 1			Tsukuba Cohort 2			Hokkaido Cohort			Meta-analysis		
	n	LogIgE	P value	n	LogIgE	P value	n	LogIgE	P value	N	LogIgE	P value
(A) The model adjusted for age, gender, and smoking status.												
CC	72	1.69 (1.56–1.81)	0.12	32	1.66 (1.45–1.87)	0.018	73	1.62 (1.48–1.77)	0.029	177	1.65 (1.57–1.74)	0.00033
CT	406	1.70 (1.65–1.75)		204	1.90 (1.82–1.98)		298	1.82 (1.75–1.89)		908	1.79 (1.75–1.82)	
TT	489	1.77 (1.72–1.82)		277	1.97 (1.90–2.04)		478	1.83 (1.77–1.89)		1244	1.84 (1.80–1.87)	
(B) The model adjusted for age, gender, smoking status, and allergic sensitization.												
CC	72	1.65 (1.53–1.76)	0.026	32	1.62 (1.44–1.81)	0.0040	73	1.68 (1.55–1.81)	0.12	177	1.65 (1.57–1.73)	0.000063
CT	406	1.70 (1.66–1.75)		204	1.92 (1.85–2.00)		298	1.81 (1.75–1.88)		908	1.79 (1.76–1.83)	
TT	489	1.77 (1.73–1.82)		277	1.96 (1.89–2.02)		477	1.82 (1.77–1.87)		1243	1.83 (1.80–1.86)	

IgE, Immunoglobulin E.
Data are presented as estimated marginal average mean (95% CI) or n.

Table 5
Association between rs7216389 and the allergic sensitization in combined healthy and asthmatic individuals.

Genotype	Tsukuba Cohort 1			Tsukuba Cohort 2			Hokkaido Cohort			Meta-analysis		
	Atopy (%)	OR (95% CI)	*P* value	Atopy (%)	OR (95% CI)	*P* value	Atopy (%)	OR (95% CI)	*P* value	Atopy (%)	OR (95% CI)	*P* value
CC	56 (62.9)	0.81	0.054	37 (69.8)	0.94	0.67	63 (52.1)	0.98	0.87	156 (59.3)	0.91	0.14
CT	283 (58.7)	(0.65–1.003)		224 (65.3)	(0.72–1.24)		283 (59.2)	(0.81–1.19)		790 (60.6)	(0.80–1.03)	
TT	356 (58.6)			318 (69.4)			504 (59.8)			1178 (61.7)		

OR, Odds ratio; CI, Confidence interval.
The analysis was adjusted for age, gender, smoking status, total serum IgE (log-transformed), and asthma affliction status.

Table 6
Association between rs7216389 and total serum IgE (log-transformed) in combined healthy and asthmatic individuals.

Genotype	Tsukuba Cohort 1			Tsukuba Cohort 2			Hokkaido Cohort			Meta-analysis		
	n	Log IgE	P value	n	Log IgE	P value	n	Log IgE	P value	N	Log IgE	P value
CC	89	1.72 (1.62–1.83)	0.012	53	1.80 (1.65–1.94)	0.0014	121	1.93 (1.83–2.03)	0.11	263	1.83 (1.76–1.90)	0.000017
CT	482	1.80 (1.75–1.84)		343	2.04 (1.98–2.09)		478	1.98 (1.93–2.03)		1303	1.93 (1.90–1.96)	
TT	608	1.86 (1.82–1.90)		458	2.08 (2.03–2.13)		843	2.03 (1.99–2.07)		1909	1.98 (1.96–2.01)	

IgE, Immunoglobulin E.
Data are presented as estimated marginal average mean (95% CI) or n. The analysis was adjusted for age, gender, smoking status, allergic sensitization, and asthma affliction status.

lymphopoietin (TSLP) expression, promoting airway inflammation in association with innate type 2 immune responses.[26,27] Furthermore, in adult patients with asthma and/or allergic rhinitis, the rs7216389 genotype was associated with enhanced type-2 immunity as indicated by fractional exhaled nitric oxide levels and eosinophil counts.[28] Collectively, given that rs7216389 genotype was not associated with the presence of allergic sensitization, the *ORMLD3*/*GSDMB* genotype could be primarily involved in non-cognate IgE production and contribute to the development of asthma *via* innate type-2 immune system activation by external stimuli such as viral infections or tobacco smoke.

There is an agreement among population studies that frequent and severe wheezing in childhood is likely to continue throughout childhood and into adulthood.[29] Allergic sensitization, frequent exacerbations, and impaired lung function have also been reported to correlate with the persistent childhood-onset asthma.[30] However, few studies have examined the genetic impact of the 17q21 locus on childhood-onset adult asthma. Given that the *ORMDL3*/*GSDMB* region is a strong susceptibility locus for early childhood asthma with severe exacerbations,[31] our findings indicate that a rs7216389 genotype may provide prognostic information about the course of asthma not only for onset early in childhood but also for the persistence of asthma over the entire lifespan.

There are several limitations to this study. First, there is the potential for recall bias due to self-reported age at onset of asthma, which might have led to misclassification. Second, the choice of only one SNP (rs7216389) within *ORMLD3*/*GSDMB* may lead to the possibility that these results may not necessarily pinpoint causal variants and genes. Third, as the genotyping of the SNP was partly carried out through a GWAS, our findings may represent spurious associations without applying a threshold of $P < 5 \times 10^{-8}$ for significance. Fourth, some studies have reported that the sensitivities of the multiple antigen simultaneous test are lower than those of other methods of antigen-specific IgE measurement[32] including skin prick testing.[33] In addition, increased IgE responsiveness toward antigens outside of the commonly tested 14 inhaled allergens, such as *Staphylococcus aureus* enterotoxins, may underlie the significant association of the rs7216389 genotype with early-onset asthma or elevated levels of total serum IgE.[34] Therefore, in the current study, underestimation of the presence of allergic sensitization may have affected our interpretation of the results. These findings, although not definitive, contribute to the discussion about the genetic role of *ORMLD3*/*GSDMB* in asthma and may stimulate the pursuit of sufficient replication by studies in other populations.

In conclusion, the functional *ORMLD3*/*GSDMB* genotype was associated with both childhood-onset adult asthma and increased total serum IgE levels but not with IgE sensitization to common inhaled allergens. Our findings may indicate that the *ORMDL3*/*GSDMB* causally contributes to asthma by exaggerating innate non-cognate IgE production in response to environmental insults. By clarifying the effect and the mechanism of the *ORMDL3*/*GSDMB* polymorphism on asthma, the findings of the current study may

help in screening environmentally sensitive patients or those requiring appropriate therapies, such as monoclonal antibodies, to target innate IgE responses.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.alit.2020.04.009.

Conflict of interest

NH has received lecture fees and/or research funding from AstraZeneca, Boehringer Ingelheim, Daiichi-Sankyo, GlaxoSmithKline, MSD, Novartis, Ono Pharmaceutical, and Pfizer. The rest of the authors have no conflicts of interest.

Authors' contributions

HK contributed to data analysis and drafting the manuscript. HM, JK, RS, KH, HY, YY, HI, TSak, and NH contributed to the design, data analysis and drafting the manuscript. YK, JK, TN, TSai, EN, SK, TH, and MT were involved in the study conception and data interpretation. NH supervised the entire research. All authors reviewed and approved the final manuscript.

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