Heterogeneity of asthma and the risk of celiac disease in children

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ABSTRACT

Background: Although human leukocyte antigen (HLA)-DR and HLA-DQ genes and gluten play crucial roles in developing celiac disease (CD), most patients with these risk factors still do not develop CD, which indicates additional unrecognized risk factors.

Objective: To determine the association between asthma and the risk of CD in children.

Methods: We conducted a population-based retrospective case-control study in children who resided in Olmsted County, Minnesota. We identified children with CD (cases) between January 1, 1997, and December 31, 2014, and compared these with children without CD (controls) (1:2 matching). Asthma status was ascertained by using the predetermined asthma criteria (PAC) and the asthma predictive index (API). Data analysis included conditional logistic regression models and an unsupervised network analysis by using an independent phenome-wide association scan (PheWAS) data set.

Results: Although asthma status as determined by using PAC was not associated with the risk of CD (odds ratio [OR] 1.4 [95% confidence interval {CI}, 0.8–2.5]; $p = 0.2$), asthma status by using the API was significantly associated (OR 2.8 [95% CI, 1.3–6.0]; $p = 0.008$). A subgroup analysis indicated that children with both asthma as determined by using PAC and a family history of asthma had an increased risk of CD compared with those without asthma (OR 2.28 [95% CI, 1.11–4.67]; $p = 0.024$). PheWAS data showed a cluster of asthma single nucleotide polymorphisms and patients with CD.

Conclusion: A subgroup of children with asthma who also had a family history of asthma seemed to be at an increased risk of CD, and, thus, the third factor that underlies the risk of CD might be related to genetic factors for asthma. Heterogeneity of asthma plays a role in determining the risk of asthma-related comorbidity.

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Celiac disease (CD) is an autoimmune disease that results in small bowel damage *via* immunologic reaction to consuming gluten among genetically susceptible individuals. CD affects ~1% of the European population¹ and 0.71% of the U.S. population.² As seen in the literature, the overall incidence of CD has increased over time.³ Human leukocyte antigen (HLA)-DQ2 and HLA-

DQ8 genes are present in almost all patients with CD.^{4,5} However, this genetic factor, in addition to consumption of gluten (gliadin and glutenin), significantly contributes to the pathogenesis of CD.⁴ Most individuals who carry HLA-DQ2 and HLA-DQ8, and who consume gluten on a regular basis do not develop CD, which indicates the presence of additional unrecognized risk factors.^{6–8} Studies in the literature indicate that various environmental factors, such as microbiota composition, infant feeding, and factors affect paracellular permeability of enterocytes to gluten as potential contributors of CD.^{9–11}

Although a few previous studies assessed the association between asthma and the risk of CD, no previous studies examined which, if any, subgroups in children with asthma have an increased risk of CD. Given increasing data on asthma phenotypes, we wanted to explore which characteristics would contribute to an increased risk of nonatopic comorbidities, *e.g.*, CD in children with asthma. In addition, to our knowledge, there is no population-based study that applied predetermined criteria for exposure (asthma status) and disease status (CD). We conducted a population-based case-control study that included pathology-proven CD cases, two sets of controls, and two different asthma criteria.

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METHODS

Study Population and Setting

We conducted our study in Olmsted County, where medical care is self-contained, which makes it an ideal setting for population-based epidemiologic studies such as this. This study used the auspices of the Rochester Epidemiology Project (REP), which is a medical records linkage system for Olmsted County, Minnesota residents (~95%) who receive medical care from two main health care providers, including Mayo Clinic and Olmsted Medical Center.¹²

Author contributions were the following: Y.J. Juhn had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis; study concept and design: B. Patel, C.-I. Wi, R. Divekar, I. Absah, Y.J. Juhn; acquisition, analysis, or interpretation of data: B. Patel, C.-I. Wi, E. Hasassri, R. Divekar, I. Absah, E. Almallouhi, E. Ryu, K. King, Y.J. Juhn; drafting of the manuscript: B. Patel, C.-I. Wi, E. Ryu, Y.J. Juhn; first draft: B. Patel; critical revision of the manuscript for important intellectual content: B. Patel, C.-I. Wi, E. Hasassri, R. Divekar, I. Absah, E. Almallouhi, E. Ryu, K. King, Y.J. Juhn; statistical analysis: B. Patel, C.-I. Wi, E. Ryu, K. King, R. Divekar, Y.J. Juhn; administrative, technical, or material support: B. Patel, C.-I. Wi, Y.J. Juhn; and study supervision: Y.J. Juhn.

Study Design and Subjects

This was a population-based retrospective case-control study. This study was approved by the institutional review board at Mayo Clinic and Olmsted Medical Center. In this study, we identified and enrolled eligible children with CD (cases) between 1997 and 2014 who resided in Olmsted County, Minnesota,¹³ and these cases were then matched by birth year and sex to obtain their corresponding control subjects. We then compared the frequency of a history of asthma between patients in the cases and the controls.

CD Case Ascertainment

Patients with the *International Classification of Diseases, Ninth Revision* (ICD-9) code for CD (579.0) before the age of 18 years were first identified between January 1, 1997, and December 31, 2014, from the REP data set and were verified with manual chart review by applying the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition criteria (Abstractor: I.A.).^{13,14} The inclusion criteria were the following: (1) positive serology markers, such as anti-tissue transglutaminase immune globulin A; (2) confirmatory small bowel biopsy specimen that showed the characteristic histologic findings (increased intraepithelial lymphocytes, villous atrophy, and crypts hyperplasia); (3) Olmsted County residents at the time of index date (Olmsted County residency was established by the resi-

dency at the time of diagnosis); and (4) research authorization for using medical records for research. Exclusion criteria were the following: (1) non-Olmsted County residency at the time of diagnosis; (2) no research authorization for use of medical records for research; (3) patients without confirmatory small bowel biopsy for CD; and (4) other diseases that cause villous atrophy, including autoimmune enteropathy, inflammatory bowel disease, and small bowel bacterial overgrowth.

Selection of Non-CD Controls

We enrolled two sets of controls: (1) community controls (1:1 matching), and (2) laboratory controls (1:1 matching). The controls were matched by sex and birth year, had to be Olmsted County residents, and had a clinic visit within 1 year of the index date for the corresponding case (*i.e.*, the index date of the controls). The community controls were identified from the REP and included patients who met the eligibility criteria for the study, except the presence of CD (*i.e.*, without ICD-9 codes for CD). Laboratory controls were identified from the list of individuals who had undergone CD screening and who tested negative for CD based on serum tissue transglutaminase antibody. The same exclusion criteria for the controls were applied by same abstractor (I.A.) as with the CD cases.

Exposure Ascertainment (asthma status). We used two independent asthma criteria to determine asthma status to address the role of heterogeneity of asthma in study outcomes.

Asthma Ascertainment by Predetermined Asthma Criteria. The entire medical records of both patients in the cases and of the controls were reviewed to determine the presence of asthma by applying predetermined asthma criteria (PAC), which is delineated in Table 1. These criteria have been extensively used in previous studies of asthma epidemiology^{15–25} and were found to have high reliability.²⁶ In addition to determining asthma status, we also evaluated for asthma characteristics, including medication use, asthma control, risk factors for asthma, and other atopic conditions. Because most cases of probable asthma (85%) become definite asthma over time, we included both probable and definite asthma for this study.¹⁶

Asthma Ascertainment by Asthma Predictive Index. We also applied the asthma predictive index (API) to our patients in the cases and the controls. The API has been developed for predicting the future development of asthma in younger children and is delineated in Table 1.^{27,28} We applied the API to all of our subjects to determine how the API associates with CD compared with asthma diagnosed by using PAC. By applying both

Table 1 Two asthma criteria

Predetermined asthma criteria
Patients were considered to have definite asthma if a physician made a diagnosis of asthma and/or if each of the following three conditions were present; they were considered to have probable asthma if only the first two conditions were present:
1. A history of cough with wheezing and/or dyspnea or a history of cough and/or dyspnea plus wheezing on examination;
2. Substantial variability in symptoms from time to time or periods of weeks or more when symptoms were absent; and
3. Two or more of the following:
Sleep disturbance caused by nocturnal cough and wheeze,
Nonsmoker,
Nasal polyps,
Blood eosinophilia > 300/ μ L,
Positive wheal-and-flare skin test result or increased serum IgE level,
A history of hay fever or infantile eczema or cough, dyspnea, and wheezing regularly on exposure to antigen,
Pulmonary function tests that show one FEV ₁ or FVC value of <70% of predicted value and another with $\geq$ 20% improvement to an FEV ₁ of >70% of predicted value, or a methacholine challenge result that showed a $\geq$ 20% decrease in FEV ₁
A favorable clinical response to bronchodilator.
Patients were excluded from the study if any of these conditions were present:
Pulmonary function tests that showed FEV ₁ to be consistently <50% of predicted value or diminished diffusion capacity;
Tracheobronchial foreign body at or about the incidence date;
Hypogammaglobulinemia (IgG level of <2.0 mg/mL) or other immunodeficiency disorder;
Wheezing that occurs only in response to anesthesia or medications;
Bullous emphysema or pulmonary fibrosis on a chest radiograph;
PiZZ α_1 -antitrypsin;
Cystic fibrosis;
Another major chest disease, such as juvenile kyphoscoliosis or bronchiectasis.
Asthma predictive index (API)*
Major criteria
1. Physician diagnosis of asthma for parents
2. Physician diagnosis of eczema for the patient
Minor criteria
1. Physician diagnosis of allergic rhinitis for the patient
2. Wheezing apart from colds
3. Eosinophilia ($\geq$ 4%)

IgE = Immunoglobulin E; FEV₁ = forced expiratory volume in 1 second; FVC = forced vital capacity.
*API (+): Frequent wheezing episodes (e.g., two or more wheezing episodes per year) plus at least one of two major criteria or two of three minor criteria.

asthma criteria (PAC and API), four subgroups were generated (i.e., PAC+, API+ [i.e., patient who met both PAC and API; group 1]; PAC+, API– [i.e., patient who met PAC, but not API; group 2]; PAC–, API+ [i.e., patients who met API, but not PAC; group 3]; and PAC–, API– [i.e., patients who did not meet PAC or API; group 4]). We assessed the association among these four groups and the risk of CD. Although CD cases were ascertained by I.A., two independent abstractors (B.P. and E.H.) ascertained the asthma status of both patients in cases and the controls by using the two criteria, after assessing

interobserver agreement for each criteria for patients in 5 sampled cases with 100% agreement.

Other Variables. Demographic variables (e.g., race, sex, age, body mass index) and a family history of asthma, atopic disease, and CD were collected. Atopic conditions and other comorbidities were also collected.

Statistical Analyses

To examine the possibility of a differential effect across different asthma criteria (i.e., heterogeneity of asthma),

Table 2 Demographics and clinical characteristics

	Celiac Disease (<i>n</i> = 94)	Controls (<i>n</i> = 188)	OR (95% CI)	<i>p</i> Value
Age, median (IQR), y	9.7 (6.5–13.1)	9.5 (6.4–13.0)		
Boys, no. (%)	37 (39)	74 (39)	—	—
White, no. (%)	84 (89)	145 (77)	3.4 (1.3–9.2)	0.012
Family history of asthma, no. (%)	25 (27)	46 (25)	1.1 (0.6–2.0)	0.69
Family history of other atopic condition, no. (%)	28 (30)	53 (28)	1.1 (0.6–1.9)	0.73
Asthma, no. (%)				
Predetermined asthma criteria	24 (26)	35 (19)	1.4 (0.8–2.5)	0.20
Asthma predictive index	18 (19)	15 (8)	2.8 (1.3–6.0)	0.008
Physician diagnosis	23 (25)	32 (17)	1.5 (0.9–2.7)	0.16
Other atopic conditions, no. (%)				
Atopic dermatitis	16 (17)	24 (13)	1.4 (0.7–2.9)	0.32
Allergic rhinitis	20 (21)	35 (19)	1.2 (0.6–2.2)	0.59
Food allergy	3 (3)	10 (5)	0.55 (0.1–2.2)	0.40
Family history of celiac disease, no. (%)	36 (38)	6 (3)	14.1 (5.5–36.0)	<0.0001
Body mass index, median (IQR), kg/m ²	16.5 (15.2–19.6)	17.1 (15.3–20.3)	0.95 (0.9–1.0)	0.27
Seasonal flu vaccine, no. (%)	49 (52)	93 (50)	1.1 (0.7–2.0)	0.63
Down Syndrome, no. (%)	4 (4)	0 (0)	—	—
Type I DM, no. (%)	7 (7)	3 (2)	4.7 (1.2–18.0)	0.026
Thyroid disease, no. (%)	3 (3)	2 (1)	30 (0.5–18.0)	0.23
Dermatitis herpetiformis, no. (%)	2 (2)	0 (0)	—	—

OR = Odds ratio; CI = confidence interval; IQR = interquartile range; DM = diabetes mellitus.

we analyzed the asthma status by using PAC and API separately and jointly as a subgroup of asthma, as described above (Asthma Ascertainment by Asthma Predictive Index). To assess a potential detection bias, we compared asthma prevalence in the control groups (community-based controls and laboratory-confirmed controls). Statistical significance was assessed with a two-sided alpha error of 0.05. Statistical analyses were performed by using the SAS software package, version 9.3 (SAS Institute, Cary, NC). As an independent exploratory analysis, we used a phenome-wide association scan (PheWAS)²⁹ to determine whether there was a significant overlap between single nucleotide polymorphisms (SNP) associated with asthma and associated comorbidities, *e.g.*, CD. We performed unsupervised bipartite network modeling to visualize co-occurring asthma SNPs and CD SNPs. The PheWAS data set³⁰ was used for this analysis.

RESULTS

Subject Characteristics

Among 266 subjects identified by the REP data set with ICD-9 codes, we included 94 study subjects after excluding 172 subjects for the following reasons; negative serology (*n* = 138), no research authorization (*n* = 8), no serology testing or biopsy (*n* = 8), positive serology result without biopsy (*n* = 7), non-Olmsted

County residents (*n* = 7), and normal biopsy results despite positive serology results (*n* = 4). Characteristics of the eligible study subjects are summarized in Table 2: 84 (89%) were white, 37 (39%) were boys, and the median age at the time of CD diagnosis was 9.7 years. Asthma prevalence by physician diagnosis, PAC, and API among community controls was 15, 17, and 6%, respectively, whereas the asthma prevalence in the laboratory controls was 19, 20, and 10%, respectively. In addition, these two control groups were similar in other clinical characteristics (*e.g.*, 24% for the presence of a family history of asthma in both control groups, 16% for well-controlled asthma in both control groups, 11 versus 14% for active asthma, 15 versus 11% for a physician diagnosis of atopic dermatitis, 17 versus 20% for physician diagnosis of allergic rhinitis, and 48 versus 51% for influenza vaccine for community versus laboratory controls, respectively).

Asthma Status and Risk of CD. We identified that those patients assessed with the API were more likely to have CD (19% versus 8%; *p* = 0.008), but asthma status by PAC was not associated with CD (26% versus 19%; *p* = 0.20) (Table 2).

Different Asthma Category (heterogeneity of asthma) and Risk of CD. Given the differential association between asthma status by using PAC and API, and the risk of

Table 3 Subgroup analysis among children with asthma by using the PAC and its related factors in relation to the risk of celiac disease

	Celiac Disease, no. (%) (<i>n</i> = 94)	Controls, no. (%) (<i>n</i> = 188)	<i>p</i> Value
Asthma and atopic conditions*			0.64
Neither	54 (57)	118 (63)	
Atopic conditions without asthma	16 (17)	35 (19)	
Asthma without atopic conditions	11 (12)	17 (9)	
Asthma with atopic conditions	13 (14)	18 (9)	
Asthma and atopy#			0.33
No asthma	70 (75)	153 (81)	
Asthma without atopy	17 (18)	28 (15)	
Asthma with atopy	7 (7)	7 (4)	
Asthma status at index date			0.32
No asthma	70 (75)	153 (82)	
Inactive asthma	6 (6)	12 (6)	
Active asthma	18 (19)	23 (12)	
Asthma onset age§			0.31
No asthma	70 (74)	153 (81)	
Asthma <6 y old	14 (15)	24 (13)	
Asthma ≥6 y old	10 (11)	11 (6)	
Asthma and family history of asthma			0.056
No asthma	70 (75)	153 (81)	
Asthma, with no family history of asthma	7 (7)	20 (11)	
Asthma, with a family history of asthma	17 (18)	15 (8)	
Asthma by using the PAC and API			0.068
Group 1 (PAC and API positive)	13 (14)	11 (6)	
Group 2 (PAC only positive)	11 (12)	24 (13)	
Group 3 (API only positive)	5 (5)	4 (2)	
Group 4 (PAC and API negative)	65 (69)	149 (79)	

PAC = Predetermined asthma criteria; API = asthma predictive index.

*Atopic conditions include physician diagnoses of allergic rhinitis and atopic dermatitis (eczema).

#Atopy was defined by allergic sensitization through a skin test or a blood test Radioallergosorbent.

§Asthma onset age in years was defined by age when the patients met PAC for the first time.

CD, we grouped the entire cohort into four subgroups by applying both asthma criteria (*i.e.*, both PAC+, API+ [group 1]); PAC+, API− [group 2]; PAC−, API+ [group 3]; and PAC−, API− [group 4]).

The results are summarized in Table 3. The strongest association between asthma and the risk of CD was found in group 1 (PAC+, API+) followed by group 3 (PAC−, API+). The main difference between API and PAC was the presence of a family history of asthma in the criteria of API, which is not part of the PAC. Thus, we re-examined the association between children with PAC+ who have a family history of asthma and the risk of CD. Although a family history of asthma *per se* did not increase the risk of CD (27% for patients with CD versus 24% for controls; *p* = 0.70), children with both asthma by PAC and a family history of asthma had, indeed, a higher risk of CD compared with those with no asthma (odds ratio 2.28 [95% confidence interval, 1.11–4.67]; *p* = 0.024).

PheWAS Analysis. All SNPs in the data set that had a Genome-wide association study association with asthma and a positive association (odds ratio > 1.0) were selected. This led to selection of 1250 SNP-disease associations. These associations are mapped as demonstrated in Fig. 1. Analysis of the results indicated that certain asthma-associated SNPs coclustered with patients with CD-related SNPs (intronic: PBX2, C6orf10, PRKG1; or intergenic: BRD2:HLA-DOA, MTCO3P1:HLA-DQA2 HLA-DRA: HLA-DRB9, DMXL2:SCG3).

DISCUSSION

Patients with API+ were more likely to have CD compared with those with API− but not patients who met other asthma criteria (*i.e.*, PAC), which indicated heterogeneity of asthma regarding an increased risk of systemic inflammatory conditions, *e.g.*, CD. Given the family history of asthma as a main difference between the API and

“SNP map” of co-occurring phenotypes with asthma

Figure 1. All single nucleotide polymorphisms (SNP) in the data set that had Genome-wide association study association with asthma and a positive association (odds ratio > 1.0) with another disease condition are depicted in the bipartite network graph. Co-occurrence of asthma SNP-associated genes (black squares) and other diagnoses (circles) are denoted by size and color of circle nodes.

the PAC, we discovered that a family history of asthma, along with a patient’s history of asthma by using PAC significantly increased the risk of CD, which indicated that a family history of asthma accounted for the differential effect of asthma criteria on the risk of CD (*i.e.*, heterogeneity). Whether this represented a phenotype of asthma associated with other nonatopic conditions would be worth investigating in future studies.

Asthma has been considered a chronic inflammatory airway disease. It is indicated in the emerging literature that asthma is a complex and multifaceted inflammatory condition and is associated with the risk of both respiratory (*e.g.*, pneumococcal infection, *Streptococcus pyogenes* upper respiratory infection, and *Bordetella pertussis*)^{31–33} and nonrespiratory infections (*e.g.*, herpes zoster and community-acquired *Escherichia coli* blood stream infection),^{34–36} which indicated that the impact of asthma status on susceptibility of infections goes beyond the airways and innate immune dysfunction of the airways.^{15,37} In addition, our group and others reported that asthma was associated with the risk of proinflammatory (*e.g.*,

coronary heart disease and diabetes mellitus)³⁸ and autoimmune conditions,^{39,40} which indicated that asthma might have a systemic inflammatory feature.

Our study findings were consistent with the known epidemiology of CD. For example, female patients had a higher risk of CD than male patients.⁴ Also, the median age of the diagnosis of CD was consistent with the literature.^{41,42} Our study findings supported that a family history of CD was the strongest risk factor for CD. A potential detection bias was an important concern to be addressed in assessing the association between asthma and the risk of CD. Although laboratory controls tended to have a slightly higher prevalence of atopic conditions, overall characteristics between community controls and laboratory controls were similar, which indicated that a differential detection of CD among patients with asthma was unlikely to explain our study results.

Children with API+, but not PAC+ had a higher risk of CD. One of the main differences of PAC from API is the absence of a family (or parental) history of asthma. Given the association between a family history of asthma

and the risk of CD among children with asthma when using PAC from subgroup analysis and the presence of a family history of asthma in the API criteria, these results strongly indicated that asthma-related genetic factors accounted for the differential effect of the two asthma criteria on the risk of CD (*i.e.*, heterogeneity). These study findings were consistent with the results from a PheWAS designed for identification of disease-gene associations²⁹ because it identified a potential cluster between asthma-associated SNPs and CD, and its associated HLA genes (*DQB1* and *DQA2*) (Fig. 1). Therefore, apart from the known HLA genes and gluten, an additional contributor to CD might have to do with asthma-related immunogenetic factors. To our knowledge, this was the first study that demonstrated a family history of asthma or genetic factors that potentially accounted for heterogeneity of asthma in relation to the risk of asthma-associated comorbidity.

These findings deserve further investigation. Recent studies showed potential associations between atopic conditions and the risk of CD,^{39,40,43} but the results have been inconsistent. For example, Pillon *et al.*⁴⁴ reported that food allergy was associated with CD in 5% of children who had severe food allergy and 0.8% of children with mild food allergy. Another study, based on a large national data set that uses ICD codes, found a potential association between asthma and the risk of CD.⁴³ However, another study found no association.⁴⁵ These previous studies had significant limitations, including use of ICD codes, which can lead to an inaccurate diagnosis of asthma,^{39,43} and detection bias, such as including only hospitalized patients.^{40,43}

It is unclear about immunogenetic pathways through which asthma operates its impact on the risk of CD. We postulated a potential immunologic link between CD and asthma through the immunologic effect of genetic factors for asthma, including interleukin (IL) 15 because IL-15 is involved with both asthma and CD. This postulation needs to be investigated in future studies. Although IL-15 was initially thought to be upregulated in predominantly Th1 cell diseases, such as rheumatoid arthritis⁴⁶ and inflammatory bowel disease,⁴⁷ results of studies demonstrated a role of IL-15 in asthma^{48,49} which has long been considered a Th2-predominant disease. Studies by Meresse *et al.*⁵⁰ and Tang *et al.*⁵¹ found that IL-15 plays a key role in amplifying this cytotoxic reaction, which is mediated by cysteinyl leukotrienes, which are involved in asthma. Although further work needs to be done to evaluate the role that IL-15 plays in these diseases, this may account for the potential association we found between asthma and CD.

Our study had a few important strengths. A population-based study design that minimized sampling bias was a major strength of our study. Also, our study setting had important epidemiologic advantages, including a self-contained health care environment and medical record linkage system through the REP, which enabled us

to capture all pertinent medical events related to both asthma status and CD. In addition, our study used two sets of predetermined asthma criteria that were previously validated and used for epidemiologic investigations for asthma. Also, our study performed an unsupervised network analysis based on the PheWAS data, which supported the study findings. Our study had inherent limitations as a retrospective study. Our study did not have pulmonary function test results or allergic sensitization tests for all the study subjects. Our study was based on a relatively small number of CD cases (underpowered), despite its population-based study design. Also, our study subjects were predominantly a white population, which may limit the generalizability to other study settings with a different ethnic composition.

CONCLUSION

A subgroup of children with asthma who also had a family history of asthma may be at an increased risk of CD, which should be replicated by future studies with a larger sample size. This finding indicated that asthma had a systemic inflammatory feature beyond the airways and that asthma-related genetic factors may account for heterogeneity of asthma in relation to the risk of CD and may provide a clue to the unknown risk factors for CD.

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