LETTER

Asthma 17q21 polymorphism associates with decreased risk of COVID-19 in children

Ioulia Gourari MD[1] | Rika Gomi MD, PhD[1] | Madeline Young BS[1] | Geancarlo Jordan BS[1] | Madeline Liongson MPH[1] | Andrea Heras MD[1] | Linda M. Gerber PhD[2] | Charlene Thomas MS[2] | Kalliope Tsirilakis MD[1] | Jennie Ono MD[3] | Pramod Narula MD[4] | Thomas Ketas BA[5] | John P. Moore PhD[5] | Stefan Worgall MD[1,6,7] | Perdita Permaul MD[1,6]

[1]Division of Pediatric Pulmonology, Allergy & Immunology, Weill Cornell Medicine, New York, New York, USA

[2]Department of Population Health Sciences, Weill Cornell Medicine, New York, New York, USA

[3]Department of Pediatrics, Weill Cornell Medicine, New York, New York, USA

[4]Department of Pediatrics, New York-Presbyterian Brooklyn Methodist Hospital, Brooklyn, New York, USA

[5]Department of Microbiology and Immunology, Weill Cornell Medicine, New York, New York, USA

[6]Drukier Institute for Children's Health, Weill Cornell Medicine, New York, New York, USA

[7]Department of Genetic Medicine, Weill Cornell Medicine, New York, New York, USA

Correspondence: Perdita Permaul, MD, Division of Pediatric Pulmonology, Allergy & Immunology, Weill Cornell Medicine, 505 East 70th St, Helmsley Tower #3F, New York, NY 10021, USA.
Email: pep9004@med.cornell.edu

To the Editor,

Infection with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) in children rarely leads to severe disease. This has been particularly surprising for children with asthma—the most common, chronic inflammatory disease in childhood. We sought to determine predictors for COVID-19 infection and symptomatic illness in children and adolescents, with and without asthma, at risk for SARS-CoV-2 across the epicenter of the ongoing pandemic in New York City (NYC).

Data collected from May 2020 through April 2021 during the early pandemic and before vaccine roll-out as part of the ongoing observational SARS-CoV-2 and Pediatric Asthma in NYC (SPAN) urban cohort study of children and adolescents were analyzed. Study participants were recruited during routine New York-Presbyterian/ Weill Cornell Medicine outpatient clinic visits across the epicenter of the COVID-19 pandemic including general pediatrics, adolescent,

pulmonary, and allergy clinics. The study population included participants aged 2–21 years without asthma and those with physician-diagnosed asthma for at least 1 year and at least one of the following: current daily preventive asthma medication use, wheezing in the past year, or an unscheduled healthcare visit for asthma in the past year. Parents/legal guardians of enrolled participants gave written informed consent. Written assent was obtained from participants aged 7–17 years. This study was approved by Institutional Review Boards at Weill Cornell Medicine, New York-Presbyterian Queens, and New York-Presbyterian Brooklyn Methodist Hospital.

A comprehensive survey administered to the parent/legal guardian included questions regarding demographics, clinical information, and exposures, specifically as it pertained to COVID-19 illness. Body mass index (BMI) was calculated using the weight data (kg) and dividing it by height (m) squared (kg/m^2). Pediatric age and

TABLE 1 Characteristics of the study population

Characteristic	Total (n = 186) No. (%)	SARS-CoV-2 uninfected (n = 118) No. (%)	SARS-CoV-2 infected (n = 68) No. (%)	p Value	Asymptomatic (n = 30) No. (%)	Symptomatic (n = 38) No. (%)	p Value
Demographics							
Age (years), median (IQR)	15·0 (12·0–17·0)	15·0 (12·0–17·0)	14·0 (11·8–17·0)	0·29	13·0 (10·0–15·8)	15·0 (13·0–18·0)	0·016
Female gender	91 (49)	59 (50)	32 (47)	0·66	12 (40)	20 (53)	0·300
Hispanic ethnicity	79 (43)	63 (54)	43 (63)	0·21	19 (63)	24 (63)	0·988
Race							
Asian	13 (7·8)	10 (9·3)	3 (5·1)	0·20	1 (3·8)	2 (6·1)	0·255
Black/African American	45 (27)	32 (30)	13 (22)		9 (35)	4 (12)	
White	40 (24)	28 (26)	12 (20)		3 (12)	9 (27)	
Annual household income <$45,000	55 (30)	36 (31)	19 (28)	0·71	11 (37)	8 (21)	0·154
Public insurance	134 (74)	82 (72)	52 (76)	0·75	26 (87)	26 (68)	0·092
Borough of residence							
Brooklyn	34 (18)	22 (19)	12 (18)	0·33	3 (10)	9 (24)	0·547
Bronx	24 (13)	17 (14)	7 (10)		3 (10)	4 (11)	
Manhattan	38 (20)	28 (24)	10 (15)		4 (14)	4 (11)	
Queens	83 (45)	48 (41)	35 (53)		18 (62)	17 (46)	
Number of household members (excluding child) (IQR)	3 (2–4)	3 (2–4)	3 (3–4)	0·35	4 (3–4)	3 (3–4)	0·428
Household member works uotside the home	108 (59)	69 (59)	39 (58)	0·92	14 (47)	25 (68)	0·085
Clinical characteristics							
Household SARS-CoV-2 exposure	38 (21)	7 (6)	31 (46)	<0·001	12 (40)	19 (50)	0·411
Environmental tobacco smoke exposure	24 (13)	15 (13)	9 (14)	0·96	1 (3·4)	8 (22)	0·066
Received flu vaccine in recent season	127 (71)	83 (72)	44 (70)	0·81	14 (54)	30 (81)	0·020
Comorbidities							
BMI category							
Nonobese (5th–<95th percentile)	117 (63)	83 (70)	34 (50)	0·006	12 (40)	22 (58)	0·143
Obese (≥95th percentile)	69 (37)	35 (30)	34 (50)		18 (60)	16 (42)	

TABLE 1 (Continued)

Characteristic	Total (n = 186) No. (%)	SARS-CoV-2 uninfected (n = 118) No. (%)	SARS-CoV-2 infected (n = 68) No. (%)	p Value	Asymptomatic (n = 30) No. (%)	Symptomatic (n = 38) No. (%)	p Value
Pre-existing asthma diagnosis	112 (60)	70 (59)	42 (62)	0·70	18·0 (60·0)	24·0 (63·0)	0·790
ICS or ICS/LABA use	63 (56)	42 (60)	21 (50)	0·30	10·0 (56·0)	11·0 (46·0)	0·533
Atopy history							
Eczema	53 (29)	33 (28)	20 (29)	0·86	10·0 (33·0)	10·0 (26·0)	0·528
Allergic rhinitis	56 (39)	34 (37)	22 (44)	0·39	7·0 (35·0)	15·0 (50·0)	0·295
Food allergy	50 (27)	33 (28)	17 (25)	0·46	8·0 (27·0)	9·0 (24·0)	0·786

Abbreviations: BMI, body mass index; ICS, inhaled corticosteroid; IQR, interquartile range; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2.

sex-adjusted BMI percentiles were then calculated using the Centers for Disease Control classification category: normal weight (5–84th BMI percentile), overweight (≥85–94th BMI percentile), and obese (≥95th BMI percentile). Blood and nasal biospecimens were collected during the participants' outpatient clinic visits.

As variations at the asthma-risk 17q21 locus are associated with ORMDL3 and Gasdermin B expression, in particular the minor risk allele (T) of single-nucleotide polymorphism (SNP) rs7216389, and strongly linked to childhood asthma and viral triggers for wheezing,[1,2] genotyping of this SNP was performed on extracted DNA using QIAamp DNA blood micro/mini kits (QIAGEN) according to manufacturer's instructions. The SNP genotyping was performed using the TaqMan® SNP Genotyping Assay (SNP ID: rs7216389). Each SNP genotyping reaction was carried out in duplicate. The SNP genotyping reaction was run in a QuantStudio 6 Flex Real-Time PCR System and the data was analyzed using QuantStudio Software (Applied Biosystems). COVID-19 infection was ascertained by positive SARS-CoV-2 specific antibodies. Immunoglobulin G antibodies against SARS-CoV-2 were determined in plasma by enzyme-linked immunosorbent assay using the SARS-CoV-2 spike protein as antigen as previously described.[3]

Descriptive statistics were calculated to characterize the SPAN cohort (Table 1). Primary outcomes of interest included: (1) positive COVID-19 serology test and (2) symptomatic COVID-19 illness defined as having a positive COVID-19 test and having at least one of the following symptoms—fever, chills, sore throat, cough, body aches, nasal congestion, rhinorrhea, loss of taste, anosmia, shortness of breath, diarrhea, vomiting, rash, and/or COVID toes, or hospitalization. Univariate logistic regression modeling calculated the unadjusted odds ratio (OR) for each of the demographic and clinical factors of interest on both outcomes, independently. A multivariate logistic regression model evaluated the independent effect of ORMDL genotype on developing COVID-19 while controlling for potential confounders such as age, inhaled corticosteroid (ICS) use, race, borough of residence, household SARS-CoV-2 exposure, and BMI. Borough of residence was included in the multivariable analysis since during the first waves of the COVID-19 pandemic in NYC (when this study was conducted), certain boroughs were particularly affected with higher numbers of infected individuals. For instance, Queens was at the epicenter early on in the pandemic. Moreover, the borough of residence might be linked to other demographic factors such as race, ethnicity, socioeconomic factors, and body mass index. Collinearity between predictors in the models was evaluated before the formulation of the final model. Ninety-five percent confidence intervals for all parameters of interest were calculated to assess the precision of the obtained estimates. All p values were two-sided with statistical significance evaluated at the 0.05 alpha level. All analyses were performed in R Version 4.0.5 (R Foundation for Statistical Computing).

Of the 186 participants enrolled, 68 (37%) were infected with SARS-CoV-2, and of these, 38 (56%) endorsed symptoms, and 2 (2.9%) were hospitalized. Sixty-nine participants were obese (37%) while 117 (63%) were nonobese (combined healthy weight and

TABLE 2 Univariate and multivariable analysis of factors associated with SARS-CoV-2 infection in NYC children (N = 186) COVID-19 prevalence is 37% (n = 68); of these, 56% endorsed symptoms (n = 38)

Variable	Positive SARS-CoV-2 infection				Symptomatic COVID-19 illness			
	Univariate analysis (N = 186)		Multivariable analysis[a] (N = 180)		Univariate analysis (N = 68)		Multivariable analysis (N = 68)	
Clinical characteristics	OR (95% CI)	p Value	OR (95% CI)	p Value	OR (95% CI)	p Value	OR (95% CI)	p Value
Age (continuous)	0.96 (0.89–1.05)	0.37	0.95 (0.86–1.05)	0.29	1.18 (1.02–1.38)	0.029	1.18 (1.00–1.41)	0.06
Obese body mass index	238 (1.21–4.78)	0.013	2.33 (1.01–5.51)	0.049	0.62 (0.20–1.81)	0.38	0.67 (0.18–2.42)	0.54
Household SARS-CoV-2 exposure	13.2 (5.63–34.9)	<0.001	13.2 (5.27–37.7)	<0.001	1.50 (0.57–4.01)	0.41	2.10 (0.66–7.13)	0.22
17q21 SNP (rs7216389)								
T/T versus (C/T or C/C) (all patients)	0.54 (0.29–0.99)	0.047	0.59 (0.28–1.23)	0.17	1.52 (0.56–4.32)	0.42	1.34 (0.40–4.55)	0.63
T/T versus (C/T or C/C) (asthma only)	0.39 (0.17–0.86)	0.021[b]	0.30 (0.10–0.86)	0.029[c]	1.30 (0.35–5.21)	0.70[d]	0.94 (0.17–5.07)	0.94[d]

Abbreviations: CI, confidence interval; NYC, New York City; OR, odds ratio; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; SNP, single-nucleotide polymorphism.

[a]Results from multivariable logistic regression models were adjusted for age, inhaled corticosteroid use, race, borough of residence, household SARS-CoV-2 exposure, and body mass index.

[b]Asthma = 111.

[c]Asthma = 108.

[d]Asthma = 42.

overweight); there was a significantly higher rate of obesity in SARS-CoV-2 infected children ($p = 0.006$) (Table 1). Children with symptomatic COVID-19 illness were older ($p = 0.016$) and had a higher rate of influenza vaccination in the recent season ($p = 0.020$) compared to participants with asymptomatic COVID-19. Multivariable logistic regression analysis showed that obesity ($p = 0.049$) and household SARS-CoV-2 exposure ($p < 0.001$) were risk factors for acquiring SARS-CoV-2 infection in all participants (asthma and nonasthma) while the T/T genotype ($p = 0.029$) was associated with decreased infection risk in asthma participants only. Increasing age ($p = 0.029$) was the only predictor associated with more symptomatic illness on univariate analysis and trended towards significance with multivariable logistic regression analysis (Table 2). We did not find an association between SNP rs7216389 and asthma status (Supporting Information: Table E1). Additionally, there were no differences in minor allele frequency by race (Supporting Information: Table E2). Since the frequency of C/C genotype is low (10%) compared to T/T (45%) and C/T (45%), consistent with findings from other pediatric cohorts,[1] comparisons were made between T/T versus C/T or C/C (Table 2, Supporting Information: Table E3).

The primary objective of this analysis was to better understand the demographic and clinical factors associated with COVID-19 infection and symptomatic illness in the pediatric population during the early pandemic before vaccine roll-out, particularly in those with asthma. Most COVID-19 pediatric investigations have been retrospective analyses of hospitalized children; thus, observational cohort studies in nonhospitalized and healthy children are essential to assess prevalence and risk for COVID-19. As such, the SPAN cohort offers unique data and exhibited a high prevalence of SARS-CoV-2 infection in the outpatient setting; almost half were asymptomatic and unaware they had contracted COVID-19. As anticipated, home contact increased the risk for infection.

Similar to adult studies, obesity was associated with an increased risk for infection[4] but was not associated with symptomatic illness. Impairment of both innate and adaptive immune responses as well as vitamin D deficiency have all been linked to obesity-related susceptibility to acquiring infections.[5] A plausible explanation for why obese BMI was not associated with symptomatic COVID-19 in our study, however, might be that children, unlike adults, do not have obesity-associated comorbidities such as hypertension, chronic kidney disease, type 2 diabetes, and cardiovascular disease which are important risk factors for severe symptomatic COVID-19 illness. Another interesting finding is that children with symptomatic COVID-19 illness were more likely to have received the influenza vaccine in the recent season contrary to recent reports suggesting that the influenza vaccination may reduce the risk of COVID-19 infection and severity.[6] A larger sample size is needed to further assess this finding. A limitation of our study is that infection was based on a positive serology test and report of COVID-19 symptoms rather than by a nasal swab test for presence of virus.

Most notably, we identified a novel association of decreased risk for COVID-19 infection to a common childhood asthma-associated 17q21 genotype. Asthma has not been a distinct risk factor for severe COVID-19 disease in children or adults,[7] and the presence of asthma and allergies may even be protective.[8] Steroid use, thought to be a factor for this protective effect,[9] was not a confounder in our cohort. This did not include an analysis of systemic steroid use as only 9 of 186 children received a short burst of an oral corticosteroid. Thus, 17q21 asthma-risk genotypes may confer a protective effect against SARS-CoV-2 infection, particularly in children with asthma. It has been demonstrated that children with 17q21 asthma-risk genotypes, such as rs7216389, have lower sphingolipid synthesis.[1,10] Recently, two sphingolipids, sphingosine, and ceramide were shown to interfere with the uptake of SARS-CoV-2 viral particles into epithelial cell lines and primary human nasal cells in culture whereby sphingosine blocked and ceramide facilitated viral entry.[11] Therefore, genetic 17q21 variations associated with asthma risk in children (T risk allele) and higher ORMDL3 expression linked to lower sphingolipid synthesis may in turn lead to decreased viral entry. Although a larger replication cohort is needed to validate our findings, our study lays the initial groundwork for uncovering a mechanism for why children with asthma are not as vulnerable to the SARS-CoV-2 virus as originally expected. Moreover, future mechanistic studies are needed to understand how asthma-associated alterations in sphingolipid levels might be implicated in COVID-19 pathology.

AUTHOR CONTRIBUTIONS

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID

Perdita Permaul https://orcid.org/0000-0002-3795-3134

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SUPPORTING INFORMATION

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