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LETTER

WILEY

Genotypes in the 17q12-q21 asthma risk locus and early-life viral wheezing illnesses

To the Editor,

Infections with rhinovirus (RV) or respiratory syncytial virus (RSV) are the two most common triggers of wheezing illnesses in preschoolers. These illnesses are leading causes of hospitalization in the early years and also represent a significant risk factor for developing childhood asthma.[1,2] While lower respiratory illnesses caused by RSV are preventable, there are no vaccines or antivirals available for RVs. This therapeutic gap highlights the critical need to identify the pathogenic mechanisms behind virus-induced wheezing illnesses and to develop new strategies for treatment or prevention.

Genetic, environmental, and personal factors contribute to the risk of preschool wheezing illnesses. These include genes that regulate immune responses and cell-surface receptors utilized by viruses. A genomic region on chromosome 17q12-q21, which encodes the genes *ORMDL3* and *GSDMB*, significantly increases the risk for viral wheeze.[3] Interestingly, this region is also the most significant and replicated locus for childhood-onset asthma,[4,5] especially in children with a history of wheeze[6] and/or RV wheeze.[3] In a combined analysis of two birth cohorts, it was unable to resolve whether relationships between 17q12-q21 genotype, viral wheezing illnesses, and childhood asthma depended on the virus causing the initial wheezing episodes.[3] Another limitation of previous studies is that they were conducted in children with genetic ancestry most similar to European populations.

We sought to address these limitations by investigating the relationships between genetic variation at the 17q12-q21 locus and early-life viral wheezing illness in children from four birth cohorts participating in the Children's Respiratory and Environment Workgroup (CREW),[7] a consortium funded by the NIH's Environmental Influences on Child Health Outcomes (ECHO) program.[8] These children are diverse with respect to ancestry, geography, and socio-demographic factors associated with asthma. We tested for associations between single nucleotide polymorphisms (SNPs) across the extended 17q12-q21 region and time to RV- and RSV-specific wheezing illness and analyzed the role of parent-reported race.

The study population consisted of 1475 children enrolled in four birth cohorts: the Tucson Children's Respiratory Study (TCRS), the Childhood Origins of Asthma study (COAST), the Urban Environment and Childhood Asthma (URECA) study, and the Infant Susceptibility to Pulmonary Infections and Asthma Following RSV Exposure (INSPIRE) study (Table 1). This work was approved by the institutional review boards at the participating institutions. SNPs were genotyped using a TaqMan assay as previously reported.[9] Because of the strong LD among SNPs within each of the three regions,[9] we selected one SNP from each region as a surrogate for other variants in those regions. To this end, we selected rs2941504 in the proximal region because it showed the least LD with the core region SNPs in CREW children who identified as White or Black[9] and was an eQTL for *PGAP3*.[10] We selected rs7216386 in the core region because it was previously associated with RV wheezing illness and is an eQTL for *GSDMB* and *ORMDL3*.[3] In the distal region, we selected rs3859192 because it had the least LD with the core region SNPs[9,11] and was an eQTL for *GSDMA*.[12] A parent or guardian provided written informed consent for their child. Parent-identified Black children comprised 32.1% of the subjects. RV wheezing illnesses occurred in 19.2% of children identified as White and 42.8% identified as Black. RSV wheezing illnesses occurred in 21.4% and 16.7% of children identified as White and Black, respectively.

To investigate genotype effects on time to first viral wheezing illness in early life, we performed time-to-event analyses separately for RV and RSV wheezing illnesses during the first 3 years of life. We stratified this analysis by race due to differences in genetic architecture in this region. European ancestry is associated with extensive linkage disequilibrium, while African ancestry is not and is associated with unique haplotypes. In the 17q12-q21 core region, the rs7216389 TT genotype has been associated with increased risk of childhood asthma.[5] In White children, rs7216389-T was associated with more children having RV wheezing events (p-value = .006; Figure 1A). For every increase in the number of T alleles (compared with the CC genotype), RV wheezing illness risk increased 46% (Cox model hazard ratio [HR] 1.46; 95% confidence interval [CI] = 1.16–1.85, Table 2). In the Black children, time to RV wheezing events was not significantly associated with rs7216389 genotype (rs7216389: HR 1.08, 95% CI = 0.83–1.40; Figure 1B). No associations were observed with rs2941504 or rs7216386.

For RSV wheezing illnesses, there was no association with rs7216389 genotype in White children (Figure 1C), while in Black children there was a nonsignificant trend for rs7216389-TT asthma-risk genotype having a longer time-to-RSV wheezing illness (p-value .054, Figure 1D). Neither the proximal-rs2941504 nor the

TABLE 1 Participating CREW Cohorts*.

	Children parent-identified as White				Children parent-identified as Black			
Cohort	**COAST**	**INSPIRE**	**TCRS**	**Total (%)**	**INSPIRE**	**URECA**	**Total (%)**	**Overall**
Subjects included, N[a]	215	394	393	1002 (67.9%)	98	375	473 (32.1%)	1475
Sex (% Boys)	57.7	52.8	50.9	53.1	54.1	51.5	52.0	52.8
RV wheezing events	62 (28.8%)	55 (14.0%)	NA	117 (19.2%)	14 (14.3%)	186 (49.6%)	200 (42.8%)	317 (29.3%)
RSV wheezing events	65 (30.2%)	88 (22.3%)	61 (15.5%)	214 (21.4%)	21 (21.4%)	58 (15.5%)	79 (16.7%)	293 (19.9%)

Abbreviations: COAST, Childhood Origins of Asthma Study; INSPIRE, Infant Susceptibility to Pulmonary Infections and Asthma Following RSV Exposure study; NA, not applicable; RSV, respiratory syncytial virus; RV, rhinovirus; TCRS, Tucson Children's Respiratory Study; URECA, Urban Environment and Childhood Asthma study; WISC, Wisconsin Infant Study Cohort.

[a]Subjects included in the analysis had 17q12-q21 genotyped, the ascertained status of RV or RSV wheezing with age up to 3 years, parent-identified race as White or Black.

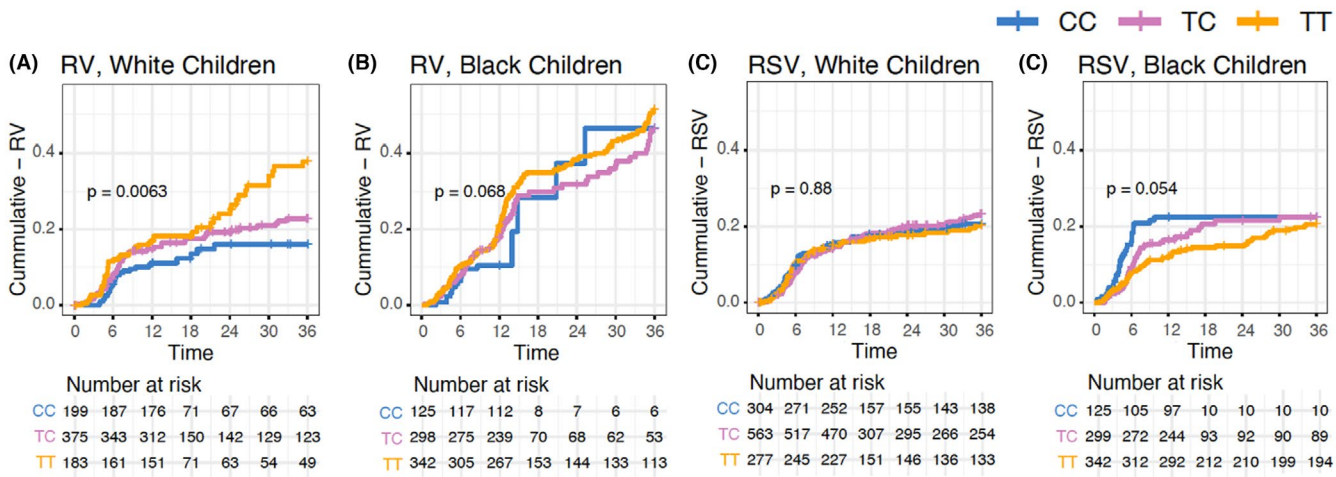

FIGURE 1 Time-to-viral wheezing illness and 17q12-q21 genotypes. Kaplan–Meier curves for time to wheezing illness for the core-rs7216389 SNP. Separate plots are shown for results stratified by virus and parent-reported race. *p* values are from the log-rank test. The numbers of children in each group at each timepoint are shown at the bottom of each panel.

TABLE 2 Cox model hazard risk[a] for time from birth to RV or RSV wheezing illness by rs7216389 T genotype.

Analysis	Hazard ratio	95% confidence interval	*p*-Value
RV – White	1.464	1.157–1.851	<.001
RV – Black	1.080	0.831–1.404	.572
RSV – White	0.984	0.816–1.185	.868
RSV – Black	1.250	0.804–1.944	.302

[a]Cox proportional hazard model included child sex, birth month, and cohort.

distal-rs3859192 region SNP was associated with RV or RSV wheezing illnesses in either White children or Black children (data not shown).

Previous studies have shown that variants at the 17q12-q21 locus are strongly associated with preschool wheezing illnesses, wheezing phenotypes, early-onset asthma, and asthma exacerbations and hospitalizations before the age of 5 years (reviewed in[13]). Furthermore, genotypes at the 17q12-q21 locus can modify the effects of environmental exposures, including adverse effects of environmental tobacco smoke and beneficial effects of older siblings,[6] farm animals, and pets.[14]

Our findings add to this growing literature by evaluating virus species and self-reported race as modifying factors across multiple birth cohorts. We showed that the rs7216389 asthma-risk allele of variation in the 17q12-q21 core region, but not in the proximal or distal regions, was associated with the time to first RV wheezing illness in preschoolers. These associations were significant for children identified as White for RV, but not significant for children identified as Black.

In contrast, the rs7216389 asthma-risk allele tended to be associated with a shorter time to first RSV wheeze in Black- and White-identified children. These effects may relate to differences in the pathogenesis of wheezing episodes caused by RV compared to RSV. For example, a recent study demonstrated that the rs7216389

asthma-risk genotype is associated with lower expression of interferon-inducible antiviral cytokines.[15] Because the RSV NS1 and NS2 proteins markedly inhibit interferon responses,[16] reduced interferon responses due to genetics could be a more substantial risk factor promoting severe RV illnesses.

The strengths of our study include using information from four different cohorts that include a broad demographic, availability of viral diagnostics, and prospective study designs that enabled consideration of multiple predictors and covariates. There are also limitations to consider. Using the parent-identified racial categories does not accurately capture ancestry effects but is likely to reflect exposures that correlate with identified race, including both physical and sociocultural environments. One potential explanation for the difference between these groups of children is that the precision of rs7216389 tagging the true causal variant at this locus may differ due to the different LD patterns between individuals of European and African ancestries.[5]

In conclusion, we demonstrated that the asthma risk allele at the 17q12-q21 core region is related to RV wheezing illnesses. The association with RSV, while of borderline significance, was in the other direction. These findings suggest that the pathogenic mechanisms of RV and RSV wheezing illnesses have distinct features. Given the lack of preventive treatments for RV, identifying mechanisms for RV wheezing illnesses could be an important step toward novel therapeutics.

KEYWORDS

17q12-q21, asthma, childhood, respiratory syncytial virus, rhinovirus, viral wheezing

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REFERENCES

1. Jackson DJ, Gangnon RE, Evans MD, et al. Wheezing rhinovirus illnesses in early life predict asthma development in high-risk children. *Am J Respir Crit Care Med*. 2008;178(7):667-672.
2. Rosas-Salazar C, Chirkova T, Gebretsadik T, et al. Respiratory syncytial virus infection during infancy and asthma during childhood in the USA (INSPIRE): a population-based, prospective birth cohort study. *Lancet*. 2023;401(10389):1669-1680.
3. Caliskan M, Bochkov YA, Kreiner-Moller E, et al. Rhinovirus wheezing illness and genetic risk of childhood-onset asthma. *N Engl J Med*. 2013;368(15):1398-1407.
4. Moffatt MF, Kabesch M, Liang L, et al. Genetic variants regulating ORMDL3 expression contribute to the risk of childhood asthma. *Nature*. 2007;448(7152):470-473.
5. Pividori M, Schoettler N, Nicolae DL, Ober C, Im HK. Shared and distinct genetic risk factors for childhood-onset and adult-onset asthma: genome-wide and transcriptome-wide studies. *Lancet Respir Med*. 2019;7(6):509-522.
6. Loss GJ, Depner M, Hose AJ, et al. The early development of wheeze. Environmental determinants and genetic susceptibility at 17q21. *Am J Respir Crit Care Med*. 2016;193(8):889-897.
7. Gern JE, Jackson DJ, Lemanske RF Jr, et al. The Children's respiratory and environmental workgroup (CREW) birth cohort consortium: design, methods, and study population. *Respir Res*. 2019;20(1):115.
8. Gillman MW, Blaisdell CJ. Environmental influences on child health outcomes, a research program of the National Institutes of Health. *Curr Opin Pediatr*. 2018;30(2):260-262.
9. Ober C, McKennan CG, Magnaye KM, et al. Expression quantitative trait locus fine mapping of the 17q12-21 asthma locus in African American children: a genetic association and gene expression study. *Lancet Respir Med*. 2020;8(5):482-492.
10. Halapi E, Gudbjartsson DF, Jonsdottir GM, et al. A sequence variant on 17q21 is associated with age at onset and severity of asthma. *Eur J Hum Genet*. 2010;18(8):902-908.
11. Stein MM, Thompson EE, Schoettler N, et al. A decade of research on the 17q12-21 asthma locus: piecing together the puzzle. *J Allergy Clin Immunol*. 2018;142(3):749-764.e3.
12. Hao K, Bosse Y, Nickle DC, et al. Lung eQTLs to help reveal the molecular underpinnings of asthma. *PLoS Genet*. 2012;8(11):e1003029.
13. Beigelman A, Srinivasan M, Goss CW, et al. Azithromycin to prevent recurrent wheeze following severe respiratory syncytial virus bronchiolitis. *NEJM Evid*. 2022;1(4):EVIDoa2100069.
14. Schoettler N, Dissanayake E, Craven MW, et al. New insights relating Gasdermin B to the onset of childhood asthma. *Am J Respir Cell Mol Biol*. 2022;67:430-437.
15. Jakwerth CA, Zissler UM, Oelsner M, et al. Nasal secretions trace epithelial type 2 response to allergen-specific immunotherapy. *Rhinology*. 2024;63:43-53.
16. Sedeyn K, Schepens B, Saelens X. Respiratory syncytial virus nonstructural proteins 1 and 2: exceptional disrupters of innate immune responses. *PLoS Pathog*. 2019;15(10):e1007984.