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CDHR3 gene variation and childhood bronchiolitis

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To the Editor

In a recent genome-wide association study, we found that a common single nucleotide polymorphism, rs6967330, in the gene *cadherin-related family member 3* (*CDHR3*) was associated with an asthma phenotype characterized by recurrent severe exacerbations in early childhood(1). CDHR3 is a transmembrane protein with high level of expression in bronchial epithelium and the *CDHR3* variant was not associated with extra-pulmonary 'atopic' traits, such as allergic sensitization or eczema, suggesting that the underlying mechanism acts locally in the respiratory epithelium increasing the susceptibility to environmental triggers. Asthma exacerbations in early childhood are predominantly triggered by lower respiratory tract infections(2), and we hypothesized that the pathogenic mechanism of the *CDHR3* variant is related to increased susceptibility to such infections.

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Bronchiolitis is a viral respiratory infection in the first years of life characterized by asthma-like symptoms and associated with increased risk of recurrent asthma-like symptoms and asthma development later in childhood(3–5). Bronchiolitis thereby has a clinical presentation resembling the phenotype associated with the *CDHR3* variant and provides an opportunity to study the hypothesis that the causal mechanism of the *CDHR3* variant is related to increased susceptibility to viral respiratory infections. We therefore performed a case-control study analyzing the association between the rs6967330 and bronchiolitis in five geographically separate cohorts (Figure E1) including more than 700 children with bronchiolitis and 1600 healthy controls.

The participating cohorts included one Danish prospective birth cohort, the Copenhagen Prospective Studies on Asthma in Childhood 2000, ($COPSAC_{2000}$) and 4 case-control studies of bronchiolitis from Freiburg (Germany), Utrecht (Netherlands), Kuopio (Finland) and Gothenburg (Sweden). Detailed description of study populations and genotyping methods for each cohort is reported in the online supplement.

We calculated association of rs6967330 with bronchiolitis using logistic regression in an additive genotype model coding for 0, 1 or 2 doses of the asthma-risk associated allele A. Meta-analysis estimates were calculated with a random effects model using inverse variance weighting.

Participant and genotype characteristics are shown for each study in Table I. The Freiburg and Utrecht cohorts were restricted to RSV-positive cases while COPSAC had 11% RSV-negative cases and the Kuopio and Gothenburg populations had 63% and 64% RSV-negative cases, respectively. Age-at-diagnosis had a marked uneven distribution with the percentage of cases with age-at-diagnosis below 180 days varying from 83% in the Utrecht cohort to 16% in the Kuopio cohort (Figure E2). Sex was equally distributed among study populations.

There was no statistically significant association between rs6967330 and bronchiolitis in the overall meta-analysis (odds ratio (OR), 1.4[95% CI, 1.0–2.2]; p=0.08) (Table II and Figure E3A). However, a statistically significant association was seen in three of the five study populations and there was strong evidence of heterogeneity between studies (p=0.0034; I^2=74.6%).

Restricting our analysis to only RSV-positive bronchiolitis showed an even weaker association (OR 1.2 [0.9–1.7]; p=0.26) (Figure E3). In contrast, there was a large effect size and statistically significant association between the variant and RSV-negative bronchiolitis (OR 2.5 [1.3–4.8], p<0.01) (Figure E3C), and this result was also significant after adjustment (Bonferroni correction) for the 5 analyses performed in the study. However, this analysis only included 58 cases and 92 controls from two studies.

Age-stratified analyses showed slightly higher effect estimate in the analysis restricted to children who were older than 6 months at hospitalization but this association was not statistically significant (Table II). An age-stratified analysis restricted to RSV-positive cases showed no indication of stronger association in older children (OR, 1.1[0.8–1.6]; p=0.44). Adjustment for sex did not change the results (Figure E3D).

A major strength of our study is the sample size, including a large proportion of RSV-positive cases allowing us to make firm conclusion about association to this, the most common, bronchiolitis presentation. However, it is a limitation of our study that we only included few children with non-RSV triggered bronchiolitis and that we did not have information on other specific triggers of bronchiolitis than RSV, particularly human rhinovirus and parainfluenza virus, which are detected in a sizable number of children hospitalized with bronchiolitis(6). A further limitation to this, and other studies of bronchiolitis, is the lack of a universal bronchiolitis definition(6). This might cause heterogeneity in case definition between studies and countries(7) which is also evident in the current study.

We found that the *CDHR3* asthma-risk variant at rs6967330 was not associated with bronchiolitis in general. Particularly, there was no association with bronchiolitis triggered by RSV infection. This lack of association was found in 4 of 5 study groups, and was not modified by age at onset of bronchiolitis. However, our results suggest that the *CDHR3* gene variant could be associated with bronchiolitis triggered by infectious agents other than RSV. For this bronchiolitis subtype, we found a considerably higher effect estimate and statistical significance in spite of a lower number of cases, indicating that the mechanism associated with the *CDHR3* variant might be virus-specific. This is supported by a recent experimental study reporting that CDHR3 functions as a rhinovirus C receptor and specifically that the *CDHR3* asthma-risk variant analyzed in our study (A allele at rs6967330) increases rhinovirus C binding and replication(8). A rhinovirus C–related mechanism fits well with our observations because rhinoviruses are common triggers of non-RSV bronchiolitis(6). Our data are also in line with a recent report of association between the *CDHR3* variant and chronic rhinosinusitis, which is often triggered by rhinoviruses(9). However, further clinical studies on the association between *CDHR3* genotype and bronchiolitis triggered by specific infectious agents, including rhinovirus subtypes, are needed to confirm such a disease mechanism.

Bronchiolitis is classically considered a single disease entity, although large variation in the clinical presentation might suggest that it is in fact a heterogeneous syndrome(5,7). Our results support such heterogeneity by showing heterogeneity in gene-association between studies and bronchiolitis subtypes. A hypothesis-free clustering approach including more than 2,600 bronchiolitis cases found that the bronchiolitis syndrome is likely to contain three to four separate phenotypes(7). One of the phenotypes identified in the above-mentioned study was dominated by rhinovirus infection, had an older age at presentation and was more frequently associated with recurrent wheezing. This phenotype resembles our RSV-negative subgroup and we hypothesize that *CDHR3* variation could partly explain clinical bronchiolitis heterogeneity through association with a specific underlying mechanism increasing the risk of rhinovirus-induced bronchiolitis and recurrent asthmatic symptoms (Figure E4).

In summary, the *CDHR3* asthma-risk variant at rs6967330 was not associated with severe RSV-bronchiolitis. However, our data indicated association with a bronchiolitis subtype triggered by other infectious agents, which should be addressed in future studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations used

CDHR3	cadherin-related family member 3
RSV	respiratory syncytial virus
COPSAC	Copenhagen Prospective Studies on Asthma in Childhood
MAF	Minor allele frequencies
OR	Odds ratio
CI	Confidence interval

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Table I

Characteristics of bronchiolitis study populations.

	COPSAC(DEN)		Kuopio(FIN)**		Gothenburg(SWE)		Freiburg(GER)		Utrecht(NED)		Combined study	
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Total cases	19	100%	63	100%	28	100%	192	100%	441	100%	743	100%
RSV positive	17	89%	21	33%	10	36%	192	100%	441	100%	681	92%
RSV negative	2	11%	40	63%	18	64%	0	0%	0	0%	60	8%
Age < 180 days	7	37%	10	16%	5	18%	124	65%	366	83%	512	69%
Age ≥ 180 days	12	63%	51	81%	23	83%	68	35%	75	17%	229	31%
Male gender	13	68%	35	56%	15	54%	124	65%	249	56%	436	59%
Total controls	305		63		29		339		911		1647	
Total population	324		128		57		530		1352		2390	
CDHR3 MAF *		0.177		0.337		0.237		0.170		0.176		0.186

* Minor allele frequency (MAF) of combined study population including both cases and controls.

** Two bronchiolitis cases from Kuopio cases had missing information on age-at-diagnosis and RSV-status. See Table E1 for details.

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Table II

Association between CDHR3 gene variation (rs6967330, A-allele) and bronchiolitis subtypes.

	COPSAC(DEN)	Kuopio(FIN)	Gothenburg(SWE)	Freiburg(GER)	Utrecht(NED)	Meta-analysis			
	OR [95% CI]	OR [95% CI]	OR [95% CI]	OR [95% CI]	OR [95% CI]	I^2	*Heterogeneity p-value*	OR [95% CI]	*p*
All bronchiolitis	2.4 [1.2–4.6]	1.8 [1.0–a3.3]	4.0 [1.4–12.6]	0.9 [0.7–1.3]	1.0 [0.8–1.2]	74.6%	<0.01	1.4 [1.0–2.2]	0.08
RSV positive	2.5 [1.2–4.9]	1.3 [0.6–2.9]	3.3 [0.8–16.0]	0.9 [0.7–1.3]	1.0 [0.8–1.2]	57.6%	0.05	1.2 [0.9–1.7]	0.26
RSV negative	*	2.1 [1.1–4.1]	4.4 [1.3–16.6]	*	*	**10.3%**	**0.29**	**2.5 [1.3–4.8]**	**0.0058**
Age < 180 days	3.2 [1.1–9.1]	0.6 [0.2–1.9]	3.3 [0.5–28.9]	1.0 [0.7–1.4]	1.0 [0.8–1.2]	44.7%	0.12	1.1 [0.8–1.6]	0.62
Age ≥ 180 days	1.9 [0.8–4.5]	2.1 [1.2–4.1]	4.2 [1.3–14.0]	0.9 [0.5–1.4]	0.9 [0.6–1.4]	64.9%	0.02	1.5 [0.9–2.4]	0.12

*no or to few cases to perform analysis.