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ORIGINAL ARTICLE

Interleukin 1 receptor-like 1 rs13408661/13431828 polymorphism is associated with persistent post-bronchiolitis asthma at school age

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Abstract

Aim: Interleukin (IL) 1 receptor-like 1, encoded by the *IL1RL1* gene, is a receptor for IL-33. In European birth cohorts, *IL1RL1* rs102082293, rs10204137 (rs4988955), rs13424006 and rs13431828 (rs13048661) variations were associated with asthma at school age. In a Dutch multi-centre study, *IL1RL1* rs1921622 variation was associated with severe bronchiolitis. We evaluated the associations of these five *IL1RL1* variations with asthma and lung function at school age after hospitalisation for bronchiolitis in infancy.

Methods: Follow-up data, including impulse oscillometry at age 5–7 and flow-volume spirometry at age 11–13 years, and the *IL1RL1* genotype data were available for 141 children followed until 5–7 and for 125 children followed until 11–13 age years after bronchiolitis in infancy. The *IL1RL1* rs10204137 and rs4988955, and the *IL1RL1* rs13048661 and rs13431828, are 100% co-segregating in the Finnish population.

Results: The variant *IL1RL1* rs13048661/13431828 genotype was constantly associated with increased asthma risk by various definitions at 5–7 and 11–13 years of ages. The result was confirmed with analyses adjusted for current confounders and early-life environment-related factors. Statistical significances were lost, when maternal asthma and atopic dermatitis in infancy were included in the model.

Conclusion: *IL1RL1* rs13048661/13431828 variation was associated with post-bronchiolitis asthma outcomes at school age.

KEYWORDS
bronchiolitis, childhood asthma, *IL1RL1* gene, lung function, polymorphism

Abbreviations: CI, confidence interval; COPSAC, Copenhagen Prospective Studies on Asthma in Childhood; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; FVS, flow-volume spirometry; ICS, inhaled corticosteroid; IL1RL1, Interleukin 1 receptor-like 1; IL-33, Interleukin-33; IOS, impulse oscillometry; MAF, minor allele frequencies; OR, odds ratio; PCR, polymerase chain reaction; PIAMA, Prevalence and Incidence of Asthma and Mite Allergy; post-BD, post-bronchodilator; Rrs5, respiratory system resistance at 5Hz; RSV, respiratory syncytial virus; ST2, suppressor of tumorigenicity-2; TIR, toll-like/interleukin-1 receptor; Xrs5, respiratory system reactance at 5Hz; zBMI, body mass index for age z-scores.

1 | INTRODUCTION

Interleukin 1 receptor-like 1 (IL1RL1), also known as suppressor of tumorigenicity-2 (ST2), is a receptor for IL-33, which is known to play a role in the pathogenesis of asthma.[1] IL1RL1 is encoded by the *IL1RL1* gene and signals via the intracellular toll-like/interleukin-1 receptor (TIR) domain.[2] The production of IL1RL1 can be assessed, for example by measuring IL1RL1-a concentration in serum.[3] The IL1RL1 was involved with the signalling of the IL-33/IL1R1 pathway, called also as IL-33/ST2 pathway, in three previous studies.[4]

The association between the severity of respiratory syncytial virus (RSV) bronchiolitis and three *IL1RL1* single nucleotide polymorphisms (SNP) rs1921622, rs11685480 and rs1420101 was studied in ventilated (severe bronchiolitis) and non-ventilated infants in a Dutch multi-centre study.[5] The *IL1RL1* rs1921622 SNP was associated with severe bronchiolitis compared with controls. In addition, severe bronchiolitis was associated with higher soluble IL1RL1-a concentrations in nasopharyngeal aspirates of the bronchiolitis patients.[5]

Genome-wide association studies have documented that the *IL1RL1* polymorphisms were associated with asthma in children attending the COPSAC (Copenhagen Prospective Studies on Asthma in Childhood) cohort.[6] The *IL1RL1* rs102082293 and rs13431828 were associated with asthma at eight years of age in the PIAMA (Prevalence and Incidence of Asthma and Mite Allergy) cohort and the *IL1LR1* rs102082293, rs10204137 and rs13424006 with asthma at the same age in the ALSPAC (Avon Longitudinal Study of Parents and Children) cohort.[7] In combined analyses, the *IL1RL1* rs102082293 and rs13424006 SNPs were associated with the phenotype of late-onset type of wheezing.[7]

We have prospectively followed, until school age, 166 children hospitalised for bronchiolitis at younger than six months of age. The control visits were arranged at the ages of 5–7 years[8] and 11–13 years.[9] As published previously from this cohort, the *IL33* rs1342326 variation was associated with severe post-bronchiolitis asthma treated with inhaled corticosteroids (ICS) at school age.[10]

The aim of the present study was to evaluate the associations of four *IL1RL1* variations, selected based on the findings of the PIAMA and ALSPAC birth cohorts, with the presence of asthma, the use of asthma medication and the presence of lung function abnormalities at ages 5–7 and 11–13 years after hospitalisation for bronchiolitis under age six months. The panel was supplemented by one SNP, which was associated with severe bronchiolitis in the Dutch multicentre bronchiolitis study.

Key Notes

- In European birth cohorts, *interleukin (IL) 1 receptor-like 1* (*IL1RL1*) variations were associated with asthma at school age.
- We found that *IL1RL1* rs13048661 and rs13431828 variations were in full linkage, and that this variation was constantly associated with post-bronchiolitis asthma at 5–7 and 11–13 years of ages.
- Examinations of *IL1RL1* rs13048661 and rs13431828 variations need to be included in future studies on genetics of bronchiolitis and post-bronchiolitis outcome.

2 | MATERIAL AND METHODS

2.1 | Design

In 2001–2004, during two separate study periods, 187 previously healthy, full-term infants younger than six months of age, were hospitalised for bronchiolitis in the Department of Pediatrics, Tampere University Hospital, Finland.[11] Demographic and clinical data collected during hospitalisation or at subsequent control visits were available from 166 patients, and blood samples were collected for genetic studies from 165 patients.

Bronchiolitis was defined as a lower respiratory tract infection associated with diffuse wheezes and/or crackles.[11] Viral aetiology of bronchiolitis was studied with antigen detection and polymerase chain reaction (PCR) in nasopharyngeal aspirates.[11] Presence of atopic dermatitis in infancy was registered during the inpatient care and at the post-bronchiolitis control visit at 1.5 years of age.[12] Data on asthma in the families, with a special focus on asthma in mothers, were obtained by interviewing the parents.

The children hospitalised for bronchiolitis in infancy were invited to attend two follow-up visits at school age. The first was arranged in 2008–2009 when the children were 5–7 years old.[8] The second was arranged in 2014–2015 when the children were 11–13 years old.[9] Before the follow-up visits, the parents completed a structured questionnaire comprising questions on doctor-diagnosed asthma and self-reported allergic rhinitis, on current use of asthma medication including ICSs and bronchodilators, and on symptoms presumptive for asthma before the control visit at age 5–7 years,[8] or respectively, after it to the present.[9] The follow-up included an interview of children and parents to check the questionnaire data.[8,9] Lung function before and after an inhalation of bronchodilator was measured with impulse oscillometry (IOS) at 5–7 years of age,[13] and with flow-volume spirometry (FVS) at 11–13 years of age.[14]

The weights and heights were recorded at both control visits, and the weight status was reported as body mass index for age *z*-scores (zBMI) using Finnish growth references.[15]

2.2 | Definitions

At the control visit at 5–7 years of age, current asthma was defined as continuous or scheduled intermittent ICS use for asthma during preceding 12 months, or alternatively, as reporting of asthma-presumptive symptoms during preceding 12 months and a diagnostic finding in the exercise challenge test.[8] Current asthma was present

in 21(12.7%) of 166 cases.[8] Allergic rhinitis was parent-reported and needed to be symptomatic during the last 12 months and was present in 48(29%) cases.[8]

At the control visit at 11–13 years of age, current asthma was defined as continuous ICS use for asthma during preceding 12 months, or alternatively, as reporting of asthma-presumptive symptoms during preceding 12 months with a diagnostic finding in the bronchodilation test.[9] In all, 138 children attended the study, and current asthma was present in 18(13.0%) cases.[9] Allergic rhinitis was parent-reported and needed to be symptomatic during the last 12 months, and was present in 60(43.5%) cases, respectively.[9]

Eleven children (8.0%) presented with persistent asthma, which means current asthma at both the 5–7 years and 11–13 years follow-up studies.[9]

2.3 | Lung function

Lung function at age 5–7 years was measured in 103 cases by IOS (Jaeger, Master Screen IOS, Höchberg, Germany), consisting of baseline, post-exercise and post-bronchodilation (0.3 mg salbutamol with a spacer) measurements, as described in detail previously.[13] The studied parameters were baseline and post-bronchodilator (post-BD) respiratory system resistance at 5Hz (Rrs5) and reactance at 5Hz (Xrs5), expressed as height-adjusted z-scores from population-based references.[13]

Lung function at age 11–13 years was measured in 89 cases with FVS (Vmax Carefusion, Becton, Dickinson and Company), consisting of baseline and post-bronchodilation (0.4 mg salbutamol with a spacer) measurements, as described in detail previously.[14] The studied parameters were baseline and post-BD forced expiratory volume in one second (FEV1) and FEV1/forced vital capacity (FEV1/FVC), expressed as sex-specific height-related of-predicted values from population-based references.[14]

2.4 | Genetics

Numerous *IL1RL1* SNPs are 100% co-segregating in the Finnish population, for example the four SNPs of rs13408661, rs10173081, rs10197862 and rs13431828 (http://ensembl.org). Thus, the genotypes of the *IL1LR1* rs13408661 we determined are identical in this cohort with the *IL1LR1* rs13431828, which was associated with childhood asthma in the PIAMA cohort.[7] Similarly, the SNPs of the *IL1LR1* rs4988955, rs4988956, rs4988957, rs10192036, rs10204137, rs4988958, rs10192157, rs10206753, rs3755276 and rs7558339 are 100% co-segregating (http://ensembl.org). Thus, the genotypes of the *IL1LR1* rs4988955 we determined are identical in this cohort with the *IL1LR* rs10204137, which was associated with childhood asthma in the ALSPAC cohort.[7]

Five SNPs, as presented in Table S1, were studied with PCR-based sequencing. Invitrogen Platinium Taq DNA polymerase (Thermo Fisher Scientific Inc.) was used for PCR according to the manufacturer´s instructions. The primers were designed using a Primer-Blast tool (National Center for Biotechnology Information, NCBI). The primers and annealing temperatures used in PCR are listed in Table S1. Prior the sequencing, PCR products were purified enzymatically with Thermo Scientific Exonuclease FastAP and Exo I (Thermo Fisher Scientific). Purified PCR products were sent for sequencing at Eurofins Genomics, Ebersberg, Germany.

2.5 | Controls

The controls for minor allele frequencies (MAFs) of the *IL1RL1* were obtained from the Finnish data of two publicly available databases: the 1000 Genomes Project (available at http://ensembl.org) and the Genome Aggregation Database (available at https://gnomad.broadinstitute.org).

2.6 | Statistics

Statistical analyses were performed using the Statistics Package for Social Science (SPSS 25.0, IBM Corp.). Chi-square and Fisher's exact tests, when appropriate, were used in the analyses of categorised variables. Student's *t*-test was used for normally distributed and Mann-Whitney test for non-normally distributed continuous variables. The results were expressed as frequencies, percentages, medians, means and standard deviations.

Multivariate logistic regression was used to confirm the significant findings in non-adjusted analyses on *IL1RL1* wild versus variant genotypes as risk factors for asthma outcomes at ages 5–7 years and 11–13 years. The analyses were adjusted first for age, sex and current allergic rhinitis (current confounders), then for age, sex, RSV aetiology of bronchiolitis and maternal smoking in infancy (early-life environment-related risk factors), and finally for age, sex, maternal asthma and atopic dermatitis in infancy (early-life atopy-related risk factors). The results were expressed as odds ratios (OR) and 95% confidence intervals (95% CI).

Analysis of co-variance, adjusted for RSV aetiology of bronchiolitis, maternal smoking during infancy, current asthma and current zMBI, was used for confirming the significant findings revealed in non-adjusted comparisons of IOS and FVS parameters between children with wild versus variant *ILRL1* genotypes. One study subject was excluded from the lung function analyses due to underweight at both ages (zBMI < 18).

3 | ETHICS

We obtained an informed consent from the parents including the use of samples for genetic studies on bronchiolitis and asthma risk collected during hospitalisations and at the control visits. The study was approved by the Ethics Committee of the Tampere University Hospital district, Tampere, Finland. The personal data of the study

subjects were not given to the laboratory that performed the genetic studies, the Department of Medical Microbiology and Immunology, Turku, Finland.

4 | RESULTS

The MAFs of the five determined *IL1RL1* SNPs were rather similar in the post-bronchiolitis cohort consisting of 165 cases, in the population-based Finnish data of the 1000 Genomes Project, which included 99 subjects, and in the Finnish data of Genome Aggregation Database, which included 1471–1737 subjects, depending on the SNP in question (Table S2).

The variant genotype of the *IL1RL1* rs13408661/13431828 SNP was associated with current ICS use in 141 former bronchiolitis patients at age 5–7 years (Table 1) and with persistent asthma in 123 at age 11–13 years (Table 2). There were no significant associations between the other four *IL1RL1* SNPs and asthma outcomes at 5–7 or 11–13 years of ages.

Multivariate logistic regression confirmed that the presence of the variant *IL1RL1* rs13408661/13431828 genotype was associated with increased ICS use at preschool age (Table 3). The finding was robust to adjustments with current confounders, such as allergic rhinitis, and to adjustments with early-life environment-related risk factors, such as RSV aetiology of bronchiolitis or exposure to maternal smoking. However, statistical significance was lost, when maternal asthma and early-life atopic dermatitis were included in the model (Table 3). Likewise, the presence of the variant *IL1RL1* rs13408661/13431828 genotype was associated with increased risks of current asthma and persistent asthma in early adolescence adjusted for early-life environment-related factors (Table 3).

The variant *IL1RL1* rs4988955/10204137 and rs13424006 genotypes were associated with higher baseline Rrs5 in IOS in 98 former bronchiolitis patients at 5–7 years of age (Table 4). The variant genotypes of the *IL1RLI* rs10208293 and rs13408661/13431828 were associated with lower post-BD Xrs5 compared with respective wild genotypes in adjusted analyses (Table 4). These four results were robust to adjustments with RSV aetiology of bronchiolitis, maternal smoking in infancy, current zBMI and current asthma (Data not shown).

There were no significant associations between these five studied *IL1RL1* gene variations and baseline or post-BD lung function by FVS in 82 former bronchiolitis patients at age of 11–13 years (Table 5).

5 | DISCUSSION

The present study evaluated the associations of five *IL1RL1* polymorphisms with asthma and lung function at school age after bronchiolitis in infancy in a prospective follow-up setting. The main result was that the variant genotype of the *IL1RL1* rs13408661/13431828 was associated with ICS use at age 5–7 years and with persistent asthma at age 11–13 years. The findings were robust to adjustments with current confounders such as allergic rhinitis, and to early-life environment-related factors, such

TABLE 1 Genotypes of the *IL1RL1* rs10208293, rs4988955/10204137, rs13424006, rs113408661/3431828 and rs1921622 polymorphisms in relation to asthma outcomes at early school age in 141 former bronchiolitis patients

	Follow-up at 5–7 years of age		
	Current asthma	Current ICS use	Asthma ever
***IL1RL1* genotype**	***N* = 19**	***N* = 18**	***N* = 36**
rs10208293			
Wild GG*N* = 77 (%)	8 (10.4)	7 (9.1)	18 (23.4)
Variant AG, AA *N* = 64 (%)	11 (17.2) $p = 0.239$	11 (17.2) $p = 0.151$	18 (28.1) $p = 0.520$
rs4988955/10204137			
Wild AA *N* = 49 (%)	7 (14.3)	6 (12.2)	13 (26.5)
Variant AG, GG *N* = 92 (%)	12 (13.0) $p = 0.837$	12 (13.0) $p = 0.892$	23 (25.0) $p = 0.843$
rs13424006			
Wild TT *N* = 49 (%)	7 (14.3)	6 (12.2)	13 (26.5)
Variant CT, CC *N* = 92 (%)	12 (13.0) $p = 0.837$	12 (13.0) $p = 0.892$	23 (25.0) $p = 0.843$
rs13408661/13431828			
Wild GG *N* = 99 (%)	10 (10.1)	9 (9.1)	25 (25.3)
Variant AG, AA *N* = 42 (%)	9 (21.4) $p = 0.072$	9 (21.4) $p =$ **0.045**	11 (26.2) $p = 0.907$
rs1921622			
Wild AA *N* = 30 (%)	2 (6.7)	2 (6.7)	10 (33.3)
Variant AG, GG *N* = 111 (%)	17 (15.3) $p = 0.365$	16 (14.4) $p = 0.362$	26 (23.4) $p = 0.269$

Statistical significance is expressed as bolded.

TABLE 2 Genotypes of the *IL1RL1* rs10208293, rs4988955/10204137, rs13424006, rs13408661/13431828 and rs1921622 polymorphisms in relation to asthma outcomes in early adolescence in 123 former bronchiolitis patients

	Follow-up at 10–13 years of age		
	Current asthma	Current ICS use	Persistent asthma
***IL1RL1* genotype**	***N* = 15**	***N* = 11**	***N* = 11**
rs10208293			
Wild GG *N* = 72 (%)	7 (9.7)	6 (8.3)	5 (6.9)
Variant AG, AA *N* = 51 (%)	8 (15.7) $p = 0.319$	5 (9.8) $p = 0.761$	6 (11.8) $p = 0.523$
rs4988955/10204137			
Wild AA *N* = 46 (%)	5 (10.9)	4 (8.7)	4 (8.7)
Variant AG, GG *N* = 77 (%)	10 (13.0) $p = 0.728$	7 (9.1) $p = 1.0$	7 (9.1) $p = 1.0$
rs13424006			
Wild TT *N* = 46 (%)	5 (10.9)	4 (8.7)	4 (8.7)
Variant CT, CC *N* = 77 (%)	10 (13.0) $p = 0.728$	7 (9.1) $p = 1.0$	7 (9.1) $p = 1.0$
rs13408661/13431828			
Wild GG *N* = 91 (%)	8 (8.8)	6 (6.6)	5 (5.5)
Variant AG, AA *N* = 32 (%)	7 (21.9) $p = 0.064$	5 (15.6) $p = 0.152$	6 (18.8) **$p = 0.034$**
rs1921622			
Wild AA *N* = 29 (%)	2 (6.9)	1 (3.4)	1 (3.4)
Variant AG, GG *N* = 94 (%)	13 (13.8) $p = 0.517$	10 (10.6) $p = 0.456$	10 (10.6) $p = 0.456$

Statistical significance is expressed as bolded.

TABLE 3 Multivariate logistic regression: Asthma risk in relation to presence of the variant *IL1RL1* rs13408661/13431828 genotype in logistic regression with stepwise adjustments for current confounders, early-life environment-related factors and early-life atopy-related factors

	OR (95% CI) adjusted for current confounders[1]		OR (95% CI) adjusted for early-life environment-related factors[2]		OR (95% CI) adjusted for early-life atopy-related factors[3]	
	OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Follow-up at 5–7 years						
Current asthma	2.7	0.9–7.8	2.5	0.9–7.0	1.7	0.6–5.4
Current ICS use	**2.9**	**1.0–8.6**	**2.8**	**1.0–8.0**	1.9	0.6–5.9
Asthma ever	1.0	0.4–2.3	1.0	0.4–2.3	0.6	0.2–1.5
Follow-up at 10–13 years						
Current asthma	2.4	0.7–7.8	**3.1**	**1.0–9.9**	2.2	0.7–7.3
Current ICS use	2.0	0.5–7.8	3.1	0.8–12.7	1.9	0.5–7.6
Persistent asthma	3.3	0.8–12.6	**4.7**	**1.2–18.5**	3.0	0.7–11.8

Note: Adjustments: [1]Age, gender, current rhinitis; [2]Age, gender, RSV aetiology of bronchiolitis, maternal smoking in infancy; [3]Age, gender, maternal asthma, atopic dermatitis at <12 months of age.

Abbreviations: 95% CI, 95% confidence interval; OR, odds ratio.

Statistical significance is expressed as bolded.

as RSV aetiology of bronchiolitis and exposure to maternal smoking in infancy. However, the findings lost their statistical significances, when maternal asthma and atopic dermatitis in infancy were included in the model. In previous birth cohort and post-bronchiolitis studies, asthma in mothers and atopic dermatitis in infants have been rather constantly significant risk factors for asthma in later childhood.[16,17] In the present post-bronchiolitis cohort, asthma in mothers and atopic dermatitis in infancy belonged to the strongest risk factors for asthma at 5–7 years[8] and 11–13 years[9] of ages. In addition, the variant genotype of the *IL1RLI* rs13408661/13431828 was associated with lower post-BD reactance, which suggests irreversible bronchial obstruction.

The *IL1RL1* gene locus has been associated with asthma in children in many studies,[1,6,7] but however, the contribution of different SNPs in this locus and the functional mechanisms remain unsolved.[18,19] Within the *IL1RL1* gene, the SNPs present with

TABLE 4 *IL1RL1* rs10208293, rs4988955/10204137, rs13424006, rs13408661/13431828 and rs1921622 polymorphisms in relation to baseline and post-bronchodilator lung function at preschool age in 98 former bronchiolitis patients

	Follow-up at 5–7 years of age			
	Baseline Rrs5	Post-BD Rrs5	Baseline Xrs5	Post-BD Xrs5
***IL1RL1* genotype**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
rs10208293				
Wild GG *N* = 55	−0.22 (1.0)	−1.78 (1.0)	−0.68 (1.4)	0.44 (0.6)
Variant AG, AA *N* = 43	0.15 (1.1) *p* = 0.084	−1.60 (1.0) *p* = 0.369	−0.82 (1.0) *p* = 0.555	0.16 (0.6) ***p* = 0.036**
rs4988955/10204137				
Wild AA *N* = 39	−0.34 (1.0)	−1.87 (1.0)	−0.58 (1.1)	0.37 (0.6)
Variant AG, GG *N* = 59	0.13 (1.0) ***p* = 0.031**	−1.59 (1.0) *p* = 0.183	−0.84 (1.3) *p* = 0.293	0.28 (0.7) *p* = 0.518
rs13424006				
Wild TT *N* = 39	−0.34 (1.0)	−1.87 (1.0)	−0.58 (1.1)	0.37 (0.6)
Variant CT, CC *N* = 59	0.13 (1.0) ***p* = 0.031**	−1.59 (1.0) *p* = 0.183	−0.84 (1.3) *p* = 0.293	0.28 (0.7) *p* = 0.518
rs13408661/13431828				
Wild GG *N* = 70	−0.12 (1.0)	−1.78 (0.9)	−0.72 (1.3)	0.40 (0.6)
Variant AG, AA *N* = 28	0.10 (1.2) *p* = 0.352	−1.51 (1.1) *p* = 0.224	−0.78 (1.1) *p* = 0.842	0.11 (0.7) ***p* = 0.043**
rs1921622				
Wild AA *N* = 21	−0.30 (1.0)	−1.92 (1.0)	−0.70 (0.9)	0.34 (0.7)
Variant AG, GG *N* = 77	−0.01 (1.1) *p* = 0.238	−1.64 (1.0) *p* = 0.250	−0.75 (1.3) *p* = 0.883	0.31 (0.6) *p* = 0.848

Statistical significance is expressed as bolded.

TABLE 5 *IL1RL1* rs10208293, rs10204137/4988955, rs13424006, rs13431828/ 13408661 and rs1921622 polymorphisms in relation to baseline and post-bronchodilator lung function in early adolescence in 82 former bronchiolitis patients

	Follow-up at 10–13 years of age			
	Baseline FEV1	Post-BD FEV1	Baseline FEV1/FVC	Post-BD FEV1/FVC
***IL1RL1* genotype**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
rs10208293				
Wild GG *N* = 47	88.9 (11.0)	92.3 (10.7)	93.8 (7.8)	96.6 (7.1)
Variant AG, AA *N* = 35	88.6 (10.57) *p* = 0.902	91.9 (12.3) *p* = 0.885	93.0 (8.0) *p* = 0.682	95.7 (6.2) *p* = 0.540
rs4988955/10204137				
Wild AA *N* = 30	87.5 (10.3)	91.0 (10.6)	94.8 (7.7)	97.3 (7.4)
Variant AG, GG *N* = 52	89.5 (11.1) *p* = 0.420	92.7 (11.8) *p* = 0.522	92.7 (7.9) *p* = 0.254	95.6 (6.3) *p* = 0.285
rs13424006				
Wild TT *N* = 30	87.5 (10.3)	91.0 (10.6)	94.8 (7.7)	97.3 (7.4)
Variant CT, CC *N* = 52	89.5 (11.1) *p* = 0.420	92.7 (11.8) *p* = 0.522	92.7 (7.9) *p* = 0.254	95.6 (6.3) *p* = 0.285
rs113408661/3431828				
Wild GG *N* = 59	88.6 (11.0)	92.1 (11.2)	93.9 (7.5)	96.7 (6.8)
Variant AG, AA *N* = 23	89.1 (10.6) *p* = 0.841	92.0 (12.0) *p* = 0.979	92.2 (8.7) *p* = 0.383	95.0 (6.5) *p* = 0.321
rs1921622				
Wild AA *N* = 18	84.8 (10.3)	89.2 (11.6)	92.6 (7.1)	96.4 (7.8)
Variant GA, AA *N* = 64	89.8 (10.8) *p* = 0.082	92.9 (11.2) *p* = 0.226	93.7 (8.1) *p* = 0.593	96.1 (6.5) *p* = 0.878

high co-segregating degrees (http://ensembl.org). In cell cultures, *IL1RL1* genetic signals contributed to asthma severity and eosinophilic genotypes of asthma, as assessed by *IL1RL1* mRNA expression and IL1RL1-a production[3,20] Genome-wide association studies documented that the *IL1RL1* rs1558441/102765865 was one of the five genetic variations, which were associated with asthma in children of the COPSAC cohort.[6] However, that polymorphism was not determined in the present study.

When 94 SNPs involving with the IL33/IL1RL1 pathway were studied in 2007 children participating in the PIAMA study and in 7247 children participating in the ALSPAC study. six *IL33* variations, two *IL1RL1* variations (rs10208293 and rs13424006), and six variations in the gene encoding the interleukin-1 receptor-accessory protein (IL1RAP) were associated with different childhood wheezing phenotypes.[7] The *IL1RL1* rs102082293 and rs13408661/13431828 were associated with asthma at eight years of age in the PIAMA cohort, and the *IL1LR1* rs102082293, rs10204137 and rs13424006 with asthma at the same age in the ALSPAC cohort. In addition, similar associations with school-age asthma were confirmed for three *IL33* variations but for none of the *IL1RAP* variations.[7] We selected these four *IL1RL1* SNPs for the present study, supplemented with the *IL1RL1* rs1921622, which has been associated with the severity of RSV bronchiolitis.[5] Our post-bronchiolitis finding that the variation of the *IL1RL1* rs13048661/13431828 was associated with an increased risk of severe and persistent school-age asthma and with lower post-BD reactance at 5Hz in IOS at 5–7 years are in line with each other.

Three *IL1RL1* variations were studied in 81 ventilated (severe) and 384 non-ventilated infants under 12 months of age hospitalised with RSV bronchiolitis and compared to 930 healthy controls.[5] The *IL1RL1* rs1921622 variation was associated with bronchiolitis severity. Furthermore, the concentrations of soluble IL1RL1-a in nasopharyngeal aspirates were higher in ventilated compared with non-ventilated bronchiolitis patients.[5] In the present study, the *IL1RL1* rs1921622 variation was not associated with post-bronchiolitis asthma or lung function at either 5–7 or 11–13 years of age. The result concerning lung function was unexpected, since RSV caused two-thirds of the bronchiolitis cases of our cohort and all cases needed hospitalisation. Severe bronchiolitis, especially when caused by RSV, is a known risk factor for later lung function deficits.[21]

The main limitation of the present post-bronchiolitis follow-up study at school age was the small number of cases for genetic analyses, which means a risk for type-2 statistical errors. On the contrary, there was one constant finding concerning the *IL1RL1* rs13408661/13431828 polymorphism, and the results for all other four studied polymorphisms were clearly negative. The variant genotype of the *IL1RL1* rs13408661/13431828 was associated with severe or persistent asthma at both 5–7 years and 11–13 years of ages in both univariate and multivariate analyses. The strengths of the study are the homogenous material that consisted of ethnically Finnish children hospitalised for bronchiolitis at younger than six months of age, careful registration of clinical data including data on medication for asthma at controls visits, and prospective long-term follow-up to the mean age of 11.7 years.

Our interpretation, although thus far speculative, is that genetic factors are to a great part responsible which children will develop post-bronchiolitis asthma. Maybe, the same children are prone to wheezing during rhinovirus infections. The IL1RL1/IL-33 pathway induces the production of IL-33 and further other Th2-type cytokines,[1,18] which are involved in the development of allergy and asthma. However, the emergence of post-bronchiolitis asthma is a complex process influenced by genes, viruses and various environmental factors. No doubt, Th2-oriented versus Th1-oriented immunity plays a role, but the current knowledge is not sufficient for interventions during or after bronchiolitis.

6 | CONCLUSION

We found evidence that *IL1RL1* rs13048661/13431828 variation was associated with increased post-bronchiolitis asthma risk constantly at 5–7 and 11–13 years of ages. The results were confirmed by versatile adjusted analyses, and in addition, were in line with findings from previous European birth cohorts. Future studies on asthma emergence in children should put accent to the IL1RL1/IL-33 pathway.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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