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IL33 rs1342326 gene variation is associated with allergic rhinitis at school age after infant bronchiolitis

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Running title: *IL33* polymorphism in allergic rhinitis

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ABSTRACT

Aim. Interleukin (IL)-33, encoded by the *IL33* gene, is associated with allergy and asthma. We evaluated *IL33* rs1342326 polymorphism in relation to asthma, asthma medication and allergic rhinitis after infant bronchiolitis.

Methods. *IL33* rs1342326 polymorphism was studied in children, who were hospitalised for bronchiolitis at age younger than six months, and who were prospectively followed until 5-7 years (N=141) and 11-13 years (N=125) of ages.

Results. Presence of the wild AA versus variant AC or CC genotypes of the *IL33* rs1342326 showed no significant associations with previous or current asthma at the mean ages of 6.4 or 11.7 years. However, 22.5% of children with the variant genotype used inhaled corticosteroids at the 5-7 years visit (adjusted OR 2.94, 95%CI 1.04-8.33, vs. those 8.9% with the wild genotype). The variant *IL33* rs1342326 genotype was associated with allergic rhinitis at 6.4 years (adjusted OR 2.17, 95%CI 1.01-4.76) and 11.7 years (3.23, 1.18-9.09) of ages.

Conclusion. The frequent use of asthma control medication in 6.4 years old children with *IL33* rs1342326 polymorphism suggests that this variation may increase susceptibility to severe asthma at preschool age. The *IL33* rs1342326 variant genotype was associated with a three-fold risk of allergic rhinitis at school age.

Key words: Interleukin-33, gene polymorphism, infant bronchiolitis, childhood asthma, allergic rhinitis

Key notes:

- Interleukin (IL)-33 is associated with allergy and asthma.
- In our post-bronchiolitis cohort, the variant *IL33* rs1342326 was not associated with asthma diagnosis at 6.4 or 11.7 years of ages but was associated with 2.9-fold use of inhaled corticosteroid at 6.4 years and with 2.2-fold to 3.2-fold risk of allergic rhinitis at 11.7 years of ages.
- The *IL33* rs1342326 variation increased the risks of allergic rhinitis and severe asthma in children.

INTRODUCTION

Interleukin (IL)-33 is a nuclear cytokine of the IL-1 family expressed in different cells including epithelial cells and released from damaged cells. In the airways, the release takes place from the cells damaged for example by viral infections, cigarette smoke, other air pollutants or inhaled allergens (1, 2). IL-33 has both pro-inflammatory and anti-inflammatory regulatory properties (3).

The *IL33* gene encoding IL-33 production, as well as the *IL1RL1* gene encoding the receptor for IL-33, have been associated with wheezing, asthma and asthma hospitalisations in children (4, 5). IL-33 plays an important role in T helper (Th) type-2 immunity activating for example Th2-type lymphocytes, mast cells and eosinophils leading finally to allergic diseases such as allergic rhinitis (3, 6).

The variant *IL33* rs1342326 genotype was associated with asthma risk in 200 Tunisian children (7). The variant *IL33* rs1342326 and rs928413 genotypes were associated with allergic rhinitis in 880 children from Austria, Finland, France, Germany and Switzerland at six years of age (8).

IL-33 cytokine and *IL33* mRNA have been constantly found in nasal and lung epithelium and in serum, sputum and bronchoalveolar lavage of adults with asthma (1). In allergic rhinitis, *IL33* mRNA was found in nasal epithelium and IL-33 protein in serum (6). There are less studies available on IL-33 in asthma or allergic rhinitis in children.

We have prospectively followed until school age 166 children hospitalised for bronchiolitis under six months of age, including control visits at ages of 5-7 (9) and 11-13 years (10). As published previously, *IL10* rs1800896 and *IL17A* rs2275913 variant alleles were protective from post-bronchiolitis asthma (9, 11-13).

The aim of the present study was to evaluate the association of the *IL33* rs1342326 genotypes with presence of asthma, use of asthma medication and presence of allergic rhinitis at 5-7 and 11-13 years of ages after hospitalisation for bronchiolitis in infancy.

MATERIAL AND METHODS

Design

In 2001-2004, between 1st December 2001 and 31st May 2002, and between 28th October 2002 and 31st May 2004, 187 previously healthy, full-term infants aged less than six months, were hospitalised due to bronchiolitis in the department of Paediatrics, Tampere University Hospital, Finland (14).

Appropriate clinical data collected during hospitalisations or at subsequent control visits were available from 166 patients and blood samples for genetic studies from 165 patients. Bronchiolitis was defined as a lower respiratory tract infection associated with diffuse wheezes and/or crackles (14). Viral aetiology of bronchiolitis, including respiratory syncytial virus (RSV), was studied with antigen detection and polymerase chain reaction (PCR) in nasopharyngeal aspirates (14).

Data on atopic dermatitis in children and asthma and allergy in mothers and fathers

were obtained during hospitalisation in infancy and at the control visit at 1.5 years of age (15).

Children hospitalised for bronchiolitis under six months of age were invited to two follow-up visits at 5-7 and 11-13 years of ages (9, 10). The parents completed a structured questionnaire comprising questions on doctor-diagnosed asthma, allergic rhinitis and atopic dermatitis, on previous or current use of inhaled corticosteroids (ICS) and bronchodilators, and on symptoms presumptive for asthma and allergic rhinitis. The follow-up study included an interview of parents, and an exercise challenge test using impulse oscillometry at 5-7 years of age (9) and a bronchodilation test using flow-volume spirometry at 11-13 years of age (10).

Definitions

At the control visit at 5-7 years of age, current asthma was defined as a continuous or intermittent ICS use for asthma during the last 12 months, or alternatively, as reporting of doctor-diagnosed wheezing, prolonged cough or night cough during the last 12 months and in addition, a diagnostic finding in the exercise challenge test (9). Current asthma was present in 21(12.7%) of 166 cases, and 18(10.9%) used ICSs. In adjusted analyses, non-RSV aetiology of bronchiolitis, atopic dermatitis in infancy and asthma in mothers were significant risk factors for current asthma (9). Allergic rhinitis was parent-reported but needed

to be earlier diagnosed by a doctor and to be symptomatic during the last 12 months, and such allergic rhinitis was present in 48(29%) cases (9).

At the control visit at 11-13 years of age, current asthma was defined as a continuous ICS use for asthma during the last 12 months, or alternatively, as reporting of repeated wheezing or prolonged cough or night cough during the last 12 months and in addition, a diagnostic finding in the bronchodilation test (10). Current asthma was present in 18(13.0%) of 138 cases, and 14(10.1%) used ICSs. In adjusted analyses, allergic rhinitis in children at 5-7 years of age and asthma in mothers were significant risk factors for current asthma (10). Allergic rhinitis was parent-reported but needed to be earlier diagnosed by a doctor and to be symptomatic during the last 12 months, and such allergic rhinitis was present in 60(43.5%) cases (10).

The prevalence of asthma ever before or at the 5-7 years follow-up was 45(27.1%). Eleven children (8.0%) presented with persistent asthma which meant current asthma at both the 5-7 years and 11-13 years follow-ups.

Genetics

A specific high-resolution melting analysis (HRMA) (Roche Diagnostics Light Cycler 480, Basel, Switzerland) was developed and used for genotyping of the *IL33* rs1342326.

Primers (forward 5'- CCTTTGACCCTTCAGAGCAC -3' and reverse 5'- AGAACAGTTTCCTCCTCTGAGC - 3') were designed with Primer-Blast design tool. Amplicon size was 227 bp. Three samples with known genotypes

were used to determine the proper concentration of MgCl_2 and annealing temperature for this HRMA assay. In each run reaction volume was 20 μl consisting of 3 μl genomic DNA ($\sim 8,0 \text{ ng}/\mu\text{l}$) and 17 μl of master mix (Light Cycler 480 High Resolution Melting Master) including 10 μl melting master dye and 0.2 μM of forward and reverse primers. The final concentration of MgCl_2 was set to 3 mM. HRMA reactions were run at 95°C for 10 min followed by 45 cycles at 95°C for 10 s, at 55°C for 10 s and at 72°C for 15 s, and final melting cycle conditions were as outlined by Roche. Melting for collecting fluorescence from 60°C to -95°C took place at ramp rate 0.02°C per second. In each run, known *IL33* rs1342326 standards were used.

Controls

The controls for minor allele frequencies (MAFs) of the *IL33* rs1342326 were obtained from the Finnish data of two publicly available databases: the 1000 Genomes Project (16) and the Genome Aggregation Database (<https://gnomad.broadinstitute.org>).

Statistics

Statistical analyses were performed using the Statistics Package for Social Sciences (SPSS 25.0, IBM Corp., NY, USA). Chi square and Fisher's exact tests when appropriate, were used in the analyses of categorised variables.

Student's t-test was used for continuous variables.

Logistic regression was used to evaluate the variant versus wild genotypes as risk factors for the outcomes at 5-7 years and 11-13 years of ages, as adjusted

for sex and RSV versus non-RSV aetiology of bronchiolitis, and for maternal asthma, atopic dermatitis in infancy and allergic rhinitis at 5-7 years of age by applying different combinations. The results were expressed as odds ratios (OR) and 95% confidence intervals (95%CI).

Ethics

We obtained informed parental consent, including the use of samples for genetic studies on bronchiolitis and asthma and allergy risk collected during index 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.

RESULTS

The wild AA genotype of the *IL33* rs1342326 was present in 101(71.6%) and the variant AC or CC in 40 children among those 141 who attended the study at 6.4 (mean) years of age. Only four had the homozygous variant CC genotype. The respective figures were 89(71.2%) and 36 among those 125 who attended the study at 11.7 (mean) years of age, and again, four had the homozygous

variant CC genotype. At both visits, 51% were boys and 49% girls.

MAF of the *IL33* rs1342326 was 15.6% in 141 former bronchiolitis patients (16.0% in 125 patients, respectively), compared to 13.8% in the Finnish population-based data including 99 subjects ($p=0.550$) and 15.1% in the Finnish genome aggregation data including 1735 subjects ($p=0.821$).

Presence of the wild versus variant genotype of the *IL33* rs1342326 showed no significant association with previous or current asthma at the 5-7 years control in crude analyses and in analyses adjusted for sex and RSV positivity during bronchiolitis (Table 1). The results remained negative when further adjusted for atopic dermatitis in infancy and asthma in mothers (Data not shown). However, 22.5% of children with the variant genotype had used ICSs during the last 12 months, compared to 8.9% of those with the wild genotype (adjusted OR 2.94, 95%CI 1.04-8.33). This association was lost when atopic dermatitis in infancy was added in the model but was even stronger when asthma in mothers was added (4.60, 1.47-14.4).

Presence of the wild versus variant genotype of the *IL33* rs1342326 showed no significant association with previous or current asthma or asthma medication at the 11-13 years control in crude analyses nor in analyses adjusted for sex and RSV positivity during bronchiolitis (Table 2). The results remained negative when further adjusted for atopic dermatitis in infancy and asthma in mothers.

The variant genotype of the *IL33* rs1342326 was associated with an increased risk of allergic rhinitis at 5-7 years of age (Table 1). The OR (95%CI) adjusted

for sex and RSV positivity was 2.17 (1.01-4.76). However, the association lost its significance when further adjusted for atopic dermatitis in infancy or asthma in mothers (Data not shown).

The variant genotype of the *IL33* rs1342326 was associated with an increased risk of allergic rhinitis at 11-13 years of age (Table 2). The OR (95%CI) adjusted for sex and RSV positivity was 3.23 (1.18-9.09). The association remained significant when further adjusted for atopic dermatitis in infancy (3.12, 1.02-9.56) or asthma in mothers (3.58, 1.27-10.06). However, the association lost its significance, when allergic rhinitis at 5-7 years of age was included in the model (Data not shown).

DISCUSSION

There are three main results in the present prospective, long-term follow-up study on the association of *IL33* rs1342326 polymorphism with childhood asthma or allergy after bronchiolitis in infancy. First, genotypes and minor allele frequencies were surprisingly similar in bronchiolitis patients and in publicly available Finnish control datasets. Second, there were no significant differences between children with wild versus variant *IL33* rs1342326 genotypes in presence of asthma at 5-7 or 12-13 years of ages. However, the variant genotype was associated with ICS medication for asthma at 5-7 years of age. Third, the

variant *IL33* rs1342326 genotype increased the risk of allergic rhinitis, and the finding was consistent at 5-7 and 11-13 years of ages.

The variant *IL33* rs1342326 genotype was associated with decreased asthma risk in 200 Tunisian children, but within the asthma group, variant C alleles were more common in those with severe than those with mild disease (7).

Though serum IL-33 was higher in asthmatics than in non-asthmatics, no association was seen between *IL33* rs7044343 or rs1342326 polymorphisms and serum IL-33 concentrations (7). We found that the *IL33* rs1342326 variant genotype was associated with more frequent need of ICS control therapy for asthma at early school age. Since such need means severe disease, our results are in line with those on severe versus mild asthma in Tunisian children (7).

The variant *IL33* rs1342326 and rs928413 genotypes were associated with allergic rhinitis in 880 European children, but the genotypes showed no associations with asthma (8). The study design was a cross-sectional six-year analysis of children belonging to regional birth cohorts. In the subgroup of 99 German children, regulatory Th cells were lower and *IL33* mRNA was higher in those with variant than with wild genotypes, suggesting insufficient control of allergic inflammation (8). These findings on Th cells and specific mRNA provide evidence for the functionality these two polymorphisms. In line, our prospective post-bronchiolitis follow-up showed that *IL33* rs1342326 polymorphism was consistently, and independently from early-life risk factors, associated with allergic rhinitis at school age.

Two-thirds of the 166 infants recruited in this cohort under six months of age were hospitalised due to RSV bronchiolitis (10). In a Dutch study,

polymorphisms of the *IL1LR1* gene were associated with susceptibility to severe RSV bronchiolitis (17). However, respective studies are not available for polymorphisms of the *IL33* gene, and in the present study, the number of non-RSV cases was too small for such comparisons. RSV infection induced nasal IL-33 cytokine secretion in 186 Spanish children with bronchiolitis (18). In an experimental study, such induction was higher in neonatal than in adult mice (19) and blocking of IL-33 with antibodies or use of IL-33 knockout mice inhibited RSV disease (19).

Ten percent of our bronchiolitis cases were caused by rhinoviruses, and in line with other studies (20), rhinovirus aetiology was a significant risk factor of post-bronchiolitis asthma (9). Only one study has been published on the connection between IL-33 cytokine, rhinoviruses and asthma (21). In cell cultures, exposure to IL-33 and rhinoviruses increased production of Th2-type cytokines and *IL33* mRNA in asthma patients but not controls without asthma (21).

The main limitation of the present study was the small number of cases which means a risk for type-2 statistical errors. In addition, only one polymorphism was studied, and only four cases had the homozygous variant genotype. Ninety-four polymorphisms were studied in 9254 Dutch and French children followed from birth for eight years, and none of the *IL33* gene polymorphisms were associated with bronchiolitis or transient early wheezing, but altogether eight were associated with different asthma phenotypes (4). The *IL33* rs1342326 that was included in our study was associated with persistent wheezing and early-onset asthma.

The strengths of this post-bronchiolitis study are the homogenous patient group that consisted of ethnically Finnish children hospitalised for bronchiolitis under six months of age, careful registration of clinical data during hospitalisations

and subsequent controls visits, and prospective long-term follow-up to the mean age of 11.7 years.

CONCLUSION

The *IL33* rs1342326 variant genotype increased the risk of allergic rhinitis at school age in this post-bronchiolitis cohort. In addition, we found preliminary evidence that the *IL33* rs1342326 variant genotype may be associated with severe childhood asthma. Identification of genetic risk factors associated with asthma and allergy may be useful in screening of patients who are at risk for later asthma after bronchiolitis in infancy.

Conflicts of interest: The authors declare no conflicts of interest.

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LIST OF ABBREVIATIONS

CI, confidence interval

DNA, deoxyribobucleic acid

HRMA, high-resolution melting analysis

ICS, inhaled corticosteroid

IL, interleukin

MAF, minor allele frequency

mRSN, messenger ribonucleic acid

OR, odds ratio

PCR, polymerase chain reaction

RSV, respiratory syncytial virus

Th, T helper

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Table 1. Asthma and allergic rhinitis at 5-7 years of age in relation to presence of wild versus variant genotypes of *IL33* rs1342326 polymorphism in 141 children after hospitalisation for bronchiolitis under six months of age.

Outcomes at 5-7 years of age	<i>IL33</i> wild (AA) N=101	<i>IL33</i> variant (AC+CC) N=40	Crude P	Adjusted OR (95%CI) Variant versus wild
Previous asthma # N=38	26	12	0.61	1.20 (0.53-2.70)
Inhaled steroids, last 12 months N=18	9	9	0.03	2.94 (1.04-8.33)
Current asthma N=19	12	7	0.38	1.52 (0.53-4.35)
Current allergic rhinitis N=40	24	16	0.05	2.17 (1.01-4.76)

The analyses were adjusted for sex and RSV positivity during bronchiolitis.

OR = odds ratio; CI = confidence interval.

Asthma was doctor diagnosed; allergic rhinitis was parent-reported. For more details, see the text.

Asthma before the 5-7 years study visit.

Table 2. Asthma and allergic rhinitis at 11-13 years of age in relation to presence of wild versus variant genotypes of *IL33* rs1342326 polymorphism in 125 children after hospitalisation for bronchiolitis under six months of age.

	<i>IL33</i> wild (AA) N=89	<i>IL33</i> variant (AC+CC) N=36	Crude P	Adjusted OR (95%CI) Variant versus wild
Persistent asthma # N=9	4	5	0.07	3.13 (0.73-14.3)
Inhaled steroids, last 12 months N=11	6	5	0.18	1.9 (0.53-7.14)
Current asthma N=15	9	6	0.30	1.67 (0.53-5.26)
Current allergic rhinitis N=19	9	10	0.01	3.23 (1.18-9.09)

The analyses were adjusted for sex and RSV positivity during bronchiolitis.

OR = odds ratio; CI = confidence interval.

Asthma was doctor diagnosed; allergic rhinitis was doctor-diagnosed but parent-reported. For more details, see the text.

Asthma at both the 5-7 years and 11-13 years study visits.