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Original Article

IL-17A gene polymorphism rs2275913 is associated with the development of asthma after bronchiolitis in infancy

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IL, interleukin; ICS, inhaled corticosteroids; FEV1, forced expiratory volume in 1 s; HRMA, high resolution melting analysis; LOS, length of hospital stay; MAF, minor allele frequency; PCR, polymerase chain reaction; RSV, respiratory syncytial virus

ABSTRACT

Background: Interleukin-17 (IL-17A) is a mainly pro-inflammatory cytokine, and IL-17 signaling implicates in the development of allergic asthma. The polymorphism rs2275913 in the promoter region of the *IL-17A* gene has in previous studies been associated with asthma susceptibility. The objective was to evaluate the association between *IL-17A* rs2275913 (-197G>A) polymorphism and post-bronchiolitis asthma and/or allergic rhinitis in a prospective 11–13 years post-bronchiolitis follow-up.
Methods: 166 previously healthy full-term infants, hospitalized for bronchiolitis at age less than 6 months, were invited to follow-up visits at the ages of 5–7 years and 11–13 years. Asthma diagnoses and presumptive symptoms, allergic rhinitis and use of inhaled corticosteroids (ICS) were registered. Blood samples for *IL-17A* rs2275913 (-197G>A) polymorphism were obtained during hospitalization or at the 5–7 years control visit.
Results: There were no significant differences between children with the wild GG and variant GA or AA genotype in the severity of bronchiolitis during hospitalization or in the outcomes until the age 5–7 years. At 11–13 years of age, children with the variant GA or AA genotype had significantly less often current asthma, use of ICSs during last 12 months or allergic rhinitis than those with the wild GG genotype. The ICS use during last 12 months retained the statistical significance in adjusted analyses (adjusted OR 0.25), whereas current asthma and allergic rhinitis marginally lost it.
Conclusions: The *IL-17A* rs2275913 (-197G>A) polymorphism decreased the risk of post-bronchiolitis asthma at 11–13 years of age, but not earlier in life, in the present prospective, long-term follow-up study.

Introduction

Asthma constitutes a global pediatric problem, and genetic susceptibility seems to play an important role in its development.[1] Inhaled corticosteroids (ICS) for maintenance and bronchodilators for exacerbations are the established drugs for asthma treatment. Allergic rhinitis frequently co-exists with asthma and may even share a common genetic basis.[2]

Bronchiolitis is usually caused by respiratory syncytial virus (RSV) being characterized by virus-induced inflammation of the bronchioles.[3] Infants hospitalized with bronchiolitis are at increased risk of both recurrent wheezing and childhood asthma.[3] Allergic children may present with impaired antiviral responses leading to more pronounced inflammation during respiratory infection and further to higher risk of subsequent wheezing.[4]

The interleukin-17 (IL-17) family contains six members, and among them IL-17A and IL-17F share the highest protein sequence homology.[5] The IL-17 family members are pro-inflammatory cytokines predominantly secreted by T helper 17 (Th17) cells.[6] In addition, there is evidence that IL-17A induces local Th17 cell production in RSV bronchiolitis and some autoimmune diseases.[7,8]

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Th17 cells contribute to the accumulation of both eosinophils and neutrophils in the tissue, and IL-17A may have an impact on the balance between eosinophilic and neutrophilic inflammation in the airways.[9,10] Thus, the *IL-17A* gene is a potential candidate gene for post-bronchiolitis asthma susceptibility.

We have previously followed-up 166 children hospitalized for bronchiolitis at less than 6 months of age. The control visits were organized at 5–7 years[11] and 11–13 years of ages. Blood samples for genetic studies were obtained during hospitalization and at the 5–7 years visits.[12] In previous publications from this post-bronchiolitis cohort, *IL-10* polymorphism was associated with rhinovirus etiology of bronchiolitis,[13] atopy and asthma at pre-school age,[14] and asthma and lung function reduction at early school age.[15]

The aim of this study was to evaluate the associations between *IL-17A* rs2275913 (-197G>A) polymorphism and presence of asthma, use of asthma medication or presence of allergic rhinitis at 1.5 years, 5–7 years and 11–13 years of ages after hospitalization for bronchiolitis at age less than 6 months.

Methods

Design

During two study periods in 2001–2004, 187 eligible, previously healthy, full-term infants aged less than 6 months were hospitalized due to bronchiolitis in the department of Pediatrics, Tampere University Hospital, Finland.[13] Clinical data, collected during hospitalizations or at control visits were available from 166 patients,[11] and blood samples for genetic studies were available from 165 patients.[14]

Bronchiolitis was defined as lower respiratory infection associated with diffuse wheezes and/or crackles.[13] Viral etiology of bronchiolitis was studied with antigen detection and polymerase chain reaction (PCR) in nasopharyngeal aspirates.[13] Data on disease severity, like need of supplementary oxygen and feeding support, and length of hospital stay (LOS) were recorded during the inpatient care.[13] Information on atopic dermatitis were registered at the post-bronchiolitis control visit at 1.5 years of age.[16]

The children hospitalized for bronchiolitis were later invited to two follow-up visits. The first was arranged in 2008–2009 when the children were 5–7 years old.[11] Before the visit the parents completed a structured questionnaire comprising questions on doctor-diagnosed asthma and allergic rhinitis, and previous or current use of asthma medication and symptoms presumptive for asthma. The follow-up study included an interview of parents to check the questionnaire data, and bronchial hyper-reactivity was studied in children by an exercise challenge test with impulse oscillometry.[11] In addition, data were collected on allergic rhinitis and atopic dermatitis, and on use of corticosteroids and bronchodilators.

The second follow-up visit was arranged in 2014–2015 when the children were 11–13 years old. Before the visit the parents completed a structured questionnaire comprising questions on doctor-diagnosed asthma and allergic rhinitis, and on current use of asthma medication and symptoms presumptive for asthma, from the control visit at 5–7 years of age to the present. The follow-up also included interview of children and parents to check the questionnaire data, and a bronchodilation test. The best FEV1 (forced expiratory volume in 1 s) of three blows before and 15 min after the inhalation of 400 μg salbutamol (Ventolin Evohaler 0.1 mg/dos, GlaxoSmithKline, London, UK), measured with flow-volume spirometry (Vmax® V62J Autobox, Becton, Dickinson, NJ, USA) were analyzed. An increase of 12% or more in FEV1 was regarded as a positive test result meaning a reversible airway obstruction.

Definitions

At the control visit at age 5–7 years current asthma was defined as a continuous or intermittent ICS use for asthma during preceding 12 months, or alternatively, as reporting of doctor-diagnosed episodes of wheezing, prolonged cough or night cough during the preceding 12 months and a diagnostic finding in the exercise challenge test.[11] The parent-reported use of bronchodilators and doctor-diagnosed allergic rhinitis and atopic dermatitis were recorded if symptomatic during the past 12 months.[11]

At the control visit at age 11–13 years, current asthma was considered if the child had used ICSs continuously during the last 12 months, or alternatively, if the child had suffered from repeated wheezing or prolonged cough or night cough for four or more weeks during the last 12 months and in addition had a diagnostic increase of FEV1 in the bronchodilation test. The parent-reported use of bronchodilators and doctor-diagnosed allergic rhinitis and atopic dermatitis were recorded for the past 12 months.

Persistent asthma was defined as the presence of asthma at both the 5–7 years and 11–13 years follow-up studies.

Genetics

Genotyping of extracted DNA for the *IL-17A* rs2275913 (-197G>A) gene was performed by high resolution melting analysis (HRMA) (Roche Diagnostics Light Cycler 480, Basel, Switzerland).[17] HRMA PCR reactions were run at 95 °C for 10 min followed by 45 cycles amplification at 95 °C for 10 s, at 59 °C for 10 s and at 72 °C for 15 s. After PCR process final melting cycle conditions were as outlined by Roche: first heating to 95 °C and hold for 1 min, and cooling to pre-hold temperature (40 °C) to make sure that all PCR products have re-associated. In each run, known (sequenced) *IL-17* rs2275913 standards (wild GG type, and heterozygous variant GA and homozygous variant AA types) were used as controls.

Controls

The IL17A rs2275913 genotypes were determined in 405 controls recruited from a study called Steps to children's healthy development and wellbeing (Steps), which is a prospective birth cohort study of 1827 children. The control group comprised Finnish infants aged two to three months, who had not yet been vaccinated (except for oral rotavirus vaccine), who were healthy, ethnic Finns, and who visited the study clinic from 2008 to 2010.[18] In controls, genotyping from extracted DNA was performed by Sequenom massARRAY iPlex Gold system (Sequenom, CA, USA) in the University of Eastern Finland, Kuopio, Finland.[18]

Ethics

The study was carried out in accordance with the WMA Declaration of Helsinki. We obtained informed parental consent, including the use of samples for genetic studies on bronchiolitis and asthma risk both during hospitalization and at the control visits. The protocol of 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.

Statistics

Statistical analyses were performed using the Statistic Package of Social Science (SPSS23.0, IBM, NY, USA). Chi square and Fisher's exact tests when appropriate, were used in the analyses of categorized 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, proportional frequencies, medians, means and standard deviations.

Logistic regression was used to evaluate the wild GG and variant GA or AA genotypes as risk factors for the outcomes at 5–7 years and 11–13 years of ages, first as non-adjusted, and then as adjusted for current age (continuous), sex, RSV positivity during bronchiolitis and atopic dermatitis at less than 12 months of age. The results were expressed as odds ratios (OR) and 95% confidence intervals (95% CI).

Results

Basic data

The mean age of the 165 bronchiolitis patients was 10.71 weeks (SD 6.82) during hospitalization, and 84 (50.6%) were boys. The wild genotype GG of *IL17A* rs2275913 was present in 48 (29.1%) children and the variant genotype in 117 (70.9%): GA in 87 (52.7%) and AA in 30 (18.2%) cases without any significant differences compared to controls (Table 1). The minor (A) allele frequency (MAF) was 0.45 (147/330) in the 165 bronchiolitis patients and 0.38 in controls ($p = 0.36$).

Hospitalization data

RSV was the causative agent in 113 (68.5%) cases. RSV was found in 33 (68.8%) cases if the child had the wild GG and in 81 (69.2%) if the child had the variant GA or AA genotype ($p = 0.95$). The mean LOS was 4.48 days (SD 3.19, range 0–22), being 4.61 days in children with wild GG and 3.97 days in children with variant GA or AA genotypes ($p = 0.32$).

There were no significant differences in the severity markers of bronchiolitis, including the need and duration of oxygen administration, or the need and duration of feeding support, between the children with wild GG and variant GA or AA genotypes (Data not shown).

Follow-up data at age 5–7 years

The wild genotype GG was present in 40 (28.6%) children and the variant genotype in 100 (71.4%): GA in 75 (53.6%) and AA in 25 (17.8%) cases. There were no significant differences in any wheezing, asthma or allergy parameters between children with wild GG and variant GA or AA genotypes (Table 2).

Follow-up data at age of 11–13 years

The wild genotype GG was present in 34 (27.4%) children and the variant genotype in 90 (72.6%): GA in 67 (54.0%) and AA in 23 (18.6%) cases. In non-adjusted analyses, children with the variant GA or AA genotype had significantly less often current asthma, or current allergic rhinitis, and reported less often use of ICSs in the last 12 months, compared with those with the wild GG genotype (Table 3).

In adjusted analyses, use of ICSs in the last 12 months (aOR 0.25) retained statistical significance, but current asthma, current allergic rhinitis and use of bronchodilators in last 12 months marginally lost it (Table 3).

Discussion

There are three main results in the present prospective, long-term follow-up study on the association of *IL-17A* rs275913 polymorphism with disease severity and development of asthma or allergic rhinitis in children hospitalized for bronchiolitis at age less than 6 months. First, we did not find any significant associations between the studied polymorphism and bronchiolitis severity during hospitalization or post-bronchiolitis outcome until 5–7 years of age. Second, we found a significant association between the studied polymorphism and asthma at the age of 11–13 years; asthma by different definitions was less common in those who had the variant GA or AA genotype of *IL-17A* rs2275913 polymorphism. The ICS use for asthma during the last 12 months remained as statistically significant in adjusted analyses. Third, we found some evidence for an association between the studied *IL17A* polymorphism and allergic rhinitis at 11–13 years of age.

The single nucleotide polymorphism (SNP) of *IL-17A* rs2275913 (-197G>A) in the promoter region of the *IL-17A* gene was selected

Table 1
Genotypes of IL17A rs2275913 polymorphisms in 165 children hospitalized for bronchiolitis at less than 6 months of age and in 405 population-based controls.

Genotypes	Bronchiolitis N = 165 (%)	Controls N = 405 (%)	*p* value vs. the wild GG genotype
Wild GG	48 (29.9)	146 (36.0)	–
Variant GA	87 (52.5)	181 (44.7)	0.072
Variant GA	30 (18.2)	78 (19.3)	0.563
Variant all, GA or AA	117 (70.9)	259 (64.0)	0.118
MAF	147/330 (44.5)	337/810 (38.3)	0.362

Distribution of three genotypes: $p = 0.187$ between bronchiolitis cases and controls.

Table 2
Clinical characteristic at the 5–7 years follow-up in relation to presence of the wild vs. variant genotype of IL-17A rs2275913 polymorphism.

Clinical characteristic	Wild GG genotype n = 40 (%)	Variant GA or AA genotype n = 100 (%)	*p* value	OR[†] (95% CI) for the variant genotype
Current asthma N = 19	8 (20.0)	11 (11.0) GA = 8, AA = 3	0.16	
Bronchodilators in last 12 months N = 26	11 (27.5)	15 (15.0) GA = 10, AA = 5	0.09	0.47 (0.19–1.13)
Inhaled steroids in last 12 months N = 18	8 (20.0)	10 (10.0) GA = 8, AA = 2	0.12	0.44 (0.16–1.22)
Allergic rhinitis in last 12 months N = 40	12 (30.0)	28 (28.0) GA = 20, AA = 8	0.81	0.91 (0.41–2.03)
Atopic dermatitis in last 12 months N = 42	13 (32.5)	29 (29.0) GA = 22, AA = 7	0.68	0.85 (0.39–1.87)

[†] aOR = OR adjusted for age, sex, RSV and atopy at age less than 12 months.

Table 3
Clinical characteristic at the 11–13 years follow-up in relation to presence of wild vs. variant genotype of IL-17A rs2275913 polymorphism.

Clinical characteristic	Wild GG genotype n = 34 (%)	Variant GA or AA genotype n = 90 (%)	*p* value	OR (95% CI) for the variant genotype	aOR[†] (95% CI) for the variant genotype
Current asthma N = 15	8 (23.5)	7 (7.8) GA = 7, AA = 0	**0.02**	**0.27 (0.09–0.83)**	0.32 (0.10–1.04)
Persistent asthma N = 9	5 (14.7)	4 (4.4) GA = 4, AA = 0	0.05	0.27 (0.07–1.07)	0.21 (0.04–1.02)
Inhaled steroids in last 12 months N = 11	6 (17.6)	5 (5.6) GA = 5, AA = 0	**0.04**	**0.28 (0.08–0.97)**	**0.25 (0.06–0.97)**
Bronchodilator in last 12 months N = 28	12 (35.3)	16 (17.8) GA = 11, AA = 5	**0.04**	**0.40 (0.16–0.96)**	0.44 (0.18–1.11)
Allergic rhinitis N = 19	9 (26.5)	10 (11.1) GA = 6, AA = 4	**0.03**	**0.35 (0.13–0.95)**	0.40 (0.13–1.22)
Atopic dermatitis N = 31	9 (26.5)	29 (29.0) GA = 22, AA = 7	0.82	0.90 (0.37–2.21)	0.95 (0.36–2.49)

The bold values represent that *p* values are significant at level <0.05.
[†] aOR = OR adjusted for age, sex, RSV and atopy at age less than 12 months.

based on previous studies, which suggested an association between that SNP and childhood asthma,[5,8,19] or between that SNP and asthma plus allergy.[20,21] The influence of different *IL-17A* variants on IL-17A production is still unknown, as is also the impact of the rs2275913 variant. In cell cultures, T cells from healthy individuals possessing the variant A allele of *IL-17A* rs2275913 produced more IL-17 than those without the A allele.[22] However, the result was opposite in the most recent study from Finland in 93 healthy infants aged 13 months.[18] Serum IL-17 was detectable in 6% of the variant AA homozygotes, in 33% of the variant GA heterozygotes, and in 75% of the wild GG homozygotes.

Dutch researchers combined clinical data from tracheal aspirates of bronchiolitis patients and experimental data from human cell cultures and an animal model of RSV infection and concluded that early local IL-17A production in the airways during RSV bronchiolitis facilitates neutrophil recruitment leading to neutrophilic inflammation in infant lungs.[23] Bronchiolitis, preschool asthma and severe asthma later may be merely associated with neutrophilic than eosinophilic inflammation.[24–26] IL-17A is, because of promoting neutrophil mobilization and further neutrophilic inflammation,[1,8] involved in host defense against bacteria, and possibly, also against viruses.[9]

The variant *IL-17A* genotypes were associated with a decreased risk of childhood asthma in a Tunisian case–control study,[5] which is in agreement with our results. In disagreement, the variant genotypes of *IL17A* genes were associated with an increased asthma and allergy risk in different populations,[19–21,27] including a study made in Chinese children.[8] The differences in the direction of the effect of the *IL-17A* rs2275913 SNP between our results and some other studies may be due to two reasons: first, simply ethnically different populations, or second, our selected study group with bronchiolitis in early infancy.

The prevalence of asthma is 7–9% in the child population at school age in Finland.[28] The 23.5% prevalence of current asthma was 3–4-fold in children with the wild GG *IL-17A* rs2275913 genotype and about the same (7.8%) in children with the variant GA or GG genotype in the present study. Since the polymorphism was not associated with wheezing or asthma until 5–7 years of age, the presence of the variant *IL-17A* rs2275913 genotype seemed to promote the natural tendency that many children with early-childhood asthma outgrow wheezing symptoms at school age. Evidently, asthma at preschool age and in adolescence have different risk factors, factors of innate immunity as an example.

There were certain limitations in the present study. The small number of patients means a risk of type-2 statistical error. On the other hand, we had a clear result that asthma risk was decreased at 11–13 years of age in those with variant *IL-17A* rs2275913 polymorphism, and we were able to confirm this result in analyses adjusted for relevant early-life confounding factors. Thus, the power of the study was sufficient for the conclusion that the variant-type *IL-17A* rs2275913 polymorphism is protective for post-bronchiolitis asthma in adolescence.

In conclusion, *IL-17A* rs2275913 polymorphism did not play any significant role in bronchiolitis that required hospitalization at less than 6 months, or in the post-bronchiolitis outcome until 5–7 years of age. Instead, the variant genotype of *IL-17A* rs2275913 polymorphism GA or AA was a significant protective factor for asthma in schoolchildren from the age 7 to 13 years.

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Conflict of interest
The authors have no conflict of interest to declare.

Authors' contributions
AH participated in data analyses and had responsibility for writing the manuscript. JT and QH had responsibility for the genetic analyses and they participated in writing the manuscript. EL, ST, PK and MH participated in the protocol development, patient screening and writing the manuscript. VP had responsibility for enrolling the control patients, arranging the laboratory analyses, and he participated in writing the manuscript. MK and KN had responsibility for protocol development, patient screening, data analysis and writing the manuscript. All authors read and approved the final manuscript.

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