Original Article

Association of Gene Polymorphisms in Interleukin 6 in Infantile Bronchial Asthma☆

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A B S T R A C T

Introduction: The genetic background of bronchial asthma is complex, and it is likely that multiple genes contribute to its development both directly and through gene–gene interactions. Cytokines contribute to different aspects of asthma, as they determine the type, severity and outcomes of asthma pathogenesis. Allergic asthmatics undergoing an asthmatic attack exhibit significantly higher levels of pro-inflammatory cytokines, such as interleukins and chemokines. In recent years, cytokines and their receptors have been shown to be highly polymorphic, and this prompted us to investigate interleukin 6 promoter polymorphisms at position −174 G/C (rs1800795) and at −572 G/C (rs1800796) in relation to asthma in children.

Methods: Interleukin 6 promoter polymorphisms were analyzed in bronchial asthma patients and healthy children using polymerase chain reaction-restriction fragment length polymorphism analysis.

Results: We observed a significant association between polymorphism at −174 G/C and bronchial asthma (OR=3.4, 95% CI: 2.045–5.638, P<.001). Higher associations between polymorphism at IL-6 −174 G/C and bronchial asthma were observed in atopic patients (OR=4.1, 95% CI: 2.308–7.280, P<8×10−7).

Conclusions: Interleukin 6 polymorphism is associated with bronchial asthma, particularly its atopic phenotype. Expression and secretion of interleukins in asthmatic patients may be affected by genetic polymorphisms, and could have a disease-modifying effect in the asthmatic airway and modify the therapeutic response.

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Asociación entre polimorfismos genéticos de la interleucina 6 y el asma bronquial en niños

R E S U M E N

Introducción: La base genética del asma bronquial es compleja y es probable que en su desarrollo contribuyan diversos genes a través de sus efectos principales e interacciones genéticas. Las citocinas participan en diferentes aspectos del asma, determinando el tipo, la gravedad y los resultados patogénicos. Durante las crisis, los asmáticos alérgicos muestran concentraciones significativamente más altas de citocinas proinflamatorias, tales como interleucinas y quimiocinas. En los últimos años, se ha observado que las citocinas y sus receptores son muy polimórficos, por lo que investigamos los polimorfismos del gen promotor de la interleucina 6 en las posiciones −174G/C (rs1800795) y −572G/C (rs1800796) en el asma infantil.

Métodos: Analizamos los polimorfismos del gen promotor de la interleucina 6 en pacientes con asma bronquial y niños sanos mediante el análisis de polimorfismos en la longitud de los fragmentos de restricción amplificados por reacción en cadena de la polimerasa.

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Introduction

Gene polymorphism may be responsible for changes in gene expression (increased, decreased, and no impact). Genetic variations in cytokine production could affect complex diseases such as bronchial asthma (BA) and help explain some specific BA characteristics and individual sensitivity to development of BA. Inflammation is a crucial component and a key event in the development of various diseases, including bronchial asthma. Therefore, genes coding for pro- and anti-inflammatory cytokines are possibly associated to BA development, including individual predisposition, and risk. Bronchial asthma is a multifactorial respiratory disease with chronic airway inflammation, which is regulated by a network of mutually interacting cytokines and inflammatory elements which may be determined by genetic or environmental factors. Cytokines contribute to different aspects of asthma, as they can determine the type, severity and outcomes of asthma pathogenesis. The genetic background of bronchial asthma is complex, and single nucleotide polymorphism (SNP) of not just 1 but several genes probably participates in the origin, development and persistence of BA and affects the efficacy of asthma treatment. Gene–gene interactions in combination with environmental factors are responsible for disease status. The immunologic aspects of BA are still being investigated.

Interleukin 6 (IL-6) is an early pleiotropic pro-inflammatory multifactorial cytokine with a key role in host defense. There is strong evidence supporting the central role of interleukin-6 in the inflammatory response. Many cell types, including airway epithelial cells, monocytes, macrophages, fibroblasts, endothelial cells, T lymphocytes, mast cells, adipose tissue, produce IL-6 and mediate the inflammatory as well as the stress-induced response. Interleukin 6 regulates production of adhesion molecules and induces secretion of other important cytokine release mediators, such as tumor necrosis factor and IL-1, that subsequently amplify the inflammatory cascade. The human IL-6 gene is 5 kb in length, located in the short arm 15–21 area of chromosome 7 (7p15–21), and contains 5 exons and 4 introns. Interleukin 6 signaling takes place along 2 pathways: classic signaling or trans-signaling. In classic signaling, IL-6 binds to membrane-bound interleukin 6 receptors (IL-6R) and the common cytokine receptor signal-transducing subunit glycoprotein 130 (gp130). This association triggers the dimerization of gp 130 and the activation of kinases. In the trans-signaling pathway, IL-6 binds to soluble interleukin 6 receptor (sIL-6R) and then to gp130. Interleukin 6 receptor engagement leads to activation of the JAK family of tyrosine kinases, which then stimulates multiple pathways involving ERK/MAPK, PI3K/AKT and JAK/STAT, and other signaling proteins.

The concentration of IL-6 is likely to be influenced by several environmental and genetic factors, including polymorphic sites in the IL-6 gene. Single nucleotide polymorphisms in the IL-6 promoter may result in individual variation in expression, concentration and functional activity of this interleukin, and can play a decisive role in the immunopathogenesis of various chronic inflammatory diseases. Pro-inflammatory cytokines, such as interleukin 6, play an important role in the complex pathogenesis of BA. Studies have shown that IL-6 SNPs effect gene expression and serum concentrations. Increased concentrations of IL-6 were observed in sputum or bronchoalveolar lavage fluid of asthmatic and atopic asthmatic patients. Animal studies have shown that IL-6 signaling in dendritic cells is essential for their uptake of allergens and initiation of Th2/Th17-mediated airway inflammation, and IL-6 plays an essential role in the development of allergic asthma. Three independent variants in the promoter region of the IL-6 gene have been detected. The G/C transition at position –174 (rs1800795) of the IL-6 gene is the most widely studied polymorphism in this gene. Several studies suggest that the GC genotype (wild type) is associated with greater production of IL-6. Initially, the major allele (G) of rs1800795 was found to be the higher IL-6 expressing variant. We aimed to analyze 2 promoter SNPs at position –174 G/C (rs1800795) and at –572 G/C (rs1800796). We hypothesized that these IL-6 SNPs might influence IL-6 gene transcription and serum, plasma or tissue concentrations of IL-6, and might also affect the magnitude of the inflammatory response and play a role in certain phenotypes of bronchial asthma. The aim of this study was to determine the association between IL-6 gene polymorphisms and bronchial asthma in a group of Slovak children.

Materials and Methods

Subjects

The present case control study included 264 children diagnosed with bronchial asthma and 250 children of comparable basic characteristics without bronchial asthma or any other disease as control subjects. New patients were systematically recruited from the allergy and clinical immunology outpatient clinic at the Department of Pediatrics, Comenius University of Bratislava, Jessenius Faculty of Medicine in Martin between 2008 and 2015. The clinical histories of the asthmatic children were taken using standard questionnaire categories: age, sex, exposure to tobacco smoke, and family history of asthma, wheezing, and allergy. Asthmatic children involved in the study were characterized by recurrent airways obstruction manifested by wheezing and dyspnea that was either self-limiting or resolved with bronchodilator therapy (as defined in the Global Initiative for Asthma), confirmed by specialist physicians. Children suffering from any serious internal diseases other than bronchial asthma were excluded from the study. Children suffering from acute respiratory infection or with a history of infection over the previous 4 weeks were also excluded from the study. None of the subjects smoked, and children exposed to passive smoking were excluded from the study. The pulmonary function tests were performed according to the European Respiratory Society and American Thoracic Society Task Force report on standardization of lung function testing. Forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), and peak expiratory flow (PEF) were measured by Koko DigiDoser-Spirometry (nSpire Health Inc., Louisiana, USA). In all children, we performed skin prick tests (SPT) with a panel of common inhalant allergens (Dermatophagoides pteronyssinus, Dermatophagoides farinae, cat dander, dog dander, mixed cereals, mixed grasses, mixed molds,
and mixed trees; ALK-ABELLO, Hørsholm, Denmark). An SPT with allergens was defined as positive if the mean of the longest diameter and the diameter perpendicular to it at its mid-point was ≥3 mm. All tests were performed by the same trained professional Children with at least 1 positive SPT were considered atopic. The control group were healthy volunteers (matched for sex and age) chosen on the basis of their negative history of allergic or other chronic diseases. Volunteers were randomly recruited during preventive visits to general practitioners. The Ethics Committee of Comenius University of Bratislava, Jessenius Faculty of Medicine in Martin approved the study, and informed consent was obtained and signed by the parents of all tested children.

Genotyping

Venous blood was collected into ethylenediaminetetraacetic acid-coated tubes and used for genomic DNA preparation. Genomic DNA was prepared using the Wizard® Genomic DNA purification Kit (Promega) and stored at −20 °C until genotype analysis. Two IL-6 gene polymorphisms (rs1800795 and rs1800796) were determined using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) analysis. In brief, DNA fragments containing the single nucleotide polymorphism restriction sites were amplified in 12 μl of reaction mixture containing 1 μl genomic DNA, 0.5 μl each primer (25 μM/μl), 6 μl Green Taq Master Mix, and 4 μl DNase free water. The primer sequences used for detection of IL-6 −174 G/C were: rs1800795F 5′-ATG CCA AGT GCT GAG TCA CTA-3′ and rs180095R 5′-GGA AAA TCC CAC ATT TGA TA-3′ and for IL-6 −572 G/C were: rs180096F 5′-GAG AGC CCT TGA AGT AAC TG-3′ and rs180096R 5′-AAC CAA AGA TGT TCT GAA CTG-3′. After initial denaturation at 94 °C for 5 min, 40 cycles of PCR were performed for IL-6 −174 G/C for 30 s at 94 °C, 45 s at 52.8 °C, and 1 min at 72 °C, with a final extension at 72 °C for 7 min. These steps amplified a 226 bp DNA PCR fragment that contained the −174 position. Then, the PCR product was digested with NlaIII (Ferments) for 15 min at 37 °C. When the C allele was found at the −174 position, the 226 pb PCR product was cleaved by NlaII into 2 fragments of 117 and 109 bp. When the G allele was present, the 226 bp fragment was not cleaved. The PCR cycling conditions for IL-6 −572 G/C polymorphism were as follows: 95 °C for 5 min, 35 cycles for 30 s at 95 °C, 30 s at 54 °C, and 45 s at 72 °C, with a final extension at 72 °C for 7 min. Digestion of PCR products with BsrBI (Ferments) for 15 min at 37 °C yielded 121 bp+61 bp fragments (GG), 182 bp+121 bp+61 bp fragments (GC). When the C allele was present, the 182 bp fragment was not cleaved. Digestion products were separated by electrophoresis in 2% agarose gel and visualized with ethidium bromide.

Statistical Analysis

Genotype frequencies were estimated for patients and healthy children. The results from both groups were compared using ANOVA, the Student’s t-test and Chi-squared test (χ²). The association between IL-6 polymorphisms at −174 G/C and −572 G/C and bronchial asthma was determined using the Pearson χ² test or Fisher’s exact test. The genotype distribution was examined for deviation from the Hardy–Weinberg equilibrium. To analyze the frequencies of the IL-6 genotypes in patients with bronchial asthma compared with healthy children, the odds ratio (OR) and confidence intervals (95% CI) were used. Both dominant and co-dominant models were evaluated. All P-values were considered to be statistically significant if P<0.05. Statistical analysis was performed using StatsDirect statistical package version 2.7.0.2.

Results

Basic patient characteristics, including age and gender are shown in Table 1. Genomic DNA from patients with bronchial asthma (n=264) and healthy subjects (n=250) were used to evaluate the presence of 2 promoter polymorphisms in the IL-6 gene, −174 G/C (rs1800795) and −572 G/C (rs1800796) (Table 2). Genotype frequencies were in Hardy–Weinberg equilibrium. The IL-6 −174 G/C genotypes GG, GC, and CC were found in 37.9%, 45.8%, and 16.3% of asthmatic subjects, respectively, and in 20.0%, 50.8%, and 29.2% of healthy subjects, respectively. The dominant genotype GG was around 17.9 more frequent in asthmatic patients compared to healthy subjects, and represents a risk factor for bronchial asthma (OR=3.4, 95% CI=2.045–5.638, P<0.001). We also observed a statistically significant association between the dominant G allele and bronchial asthma development (OR=1.87, 95% CI=1.455–2.390, P<0.001). The GC genotype is more frequent in healthy subjects than in asthmatics, therefore it does not seem to be a risk factor for BA. Comparing this genotype to homozygotes (dominant or variant) showed no association in asthmatics (OR=1.22, 95% CI=0.863–1.726, P=0.30).

There were no significant differences in the frequency of genotypes or alleles in IL-6 −572 G/C polymorphism between asthmatic patients and healthy subjects. The prevalence of the GG, GC, and CC genotypes were 77.7%, 18.2%, and 4.1% in patients and 75.2%, 22.4%, and 2.4% in healthy subjects, respectively (Table 2).

Genotypes with these 2 polymorphisms were not significantly associated with percentage predicted forced expiratory volume in 1 s (FEV₁) or with total serum IgE concentrations (results not shown).

We analyzed the association between IL-6 gene polymorphisms and atopy status (Table 3). The GG genotype of IL-6 −174 G/C (rs1800795) was more common in atopic patients (39.2%) compared to non-atopic (34.6%) or healthy subjects (20%), but significant differences were found between groups only when the genotypes GG, GC, and CC were compared to healthy subjects. The G allele was also the most common in atopic patients (62.6%) compared to non-atopic (56.4%) or healthy subjects (45.5%). The potential risk of association with IL-6 −572 G/C polymorphism was higher in asthma patients with atopy (Table 3). However, there was no significant difference in genotypes or allele frequency between atopic and non-atopic asthmatic patients in gene IL-6 −572 G/C.

We also observed significant differences in genotype frequencies in the double gene analysis: IL-6 −174 G/C with IL-6 −572 G/C. The association between SNPs and bronchial asthma was observed in the combination of GG+GG genotypes (OR=5.769, 95% CI=2.727–10.581, P<0.001).

### Table 1

Details of Participants–Children with Bronchial Asthma and Healthy Children.

<table>
<thead>
<tr>
<th>Data</th>
<th>Groups</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bronchial Asthma (264)</td>
<td>Control Group (250)</td>
</tr>
<tr>
<td>Gender – male</td>
<td>(N and %)</td>
<td>153</td>
</tr>
<tr>
<td>Gender – female</td>
<td>(N and %)</td>
<td>111</td>
</tr>
<tr>
<td>Age – years</td>
<td>(Mean and SD)</td>
<td>12.05 (1–18)</td>
</tr>
<tr>
<td>Atopy</td>
<td>(N and %)</td>
<td>186</td>
</tr>
</tbody>
</table>

N, number of participants; SD, standard deviation.
Table 2
Distribution of IL-6 –174 G/C (rs1800795) and IL-6 –572 G/C (rs1800796) Genotypes and Alleles and Their Association with the Risk of Bronchial Asthma.

<table>
<thead>
<tr>
<th>Genotypes</th>
<th>Bronchial Asthma (N=264)</th>
<th>Control Group (N=250)</th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N [%]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-6 –174 (rs1800795)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GG</td>
<td>100 (37.9)</td>
<td>50 (20.0)</td>
<td>3.40 (2.045–5.638)</td>
<td>1.577e–06</td>
</tr>
<tr>
<td>GC</td>
<td>121 (45.8)</td>
<td>127 (50.8)</td>
<td>1.62 (1.030–2.541)</td>
<td>.036</td>
</tr>
<tr>
<td>CC</td>
<td>43 (16.3)</td>
<td>73 (29.2)</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>GC+GC</td>
<td>164 (62.1)</td>
<td>200 (80.0)</td>
<td>2.12 (1.385–3.244)</td>
<td>.0005</td>
</tr>
<tr>
<td>Allele G</td>
<td>321 (60.8)</td>
<td>227 (45.4)</td>
<td>1.87 (1.455–2.390)</td>
<td>7.608e–07</td>
</tr>
<tr>
<td>Allele C</td>
<td>207 (39.2)</td>
<td>273 (54.6)</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>IL-6 –572 (rs1800796)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GG</td>
<td>205 (77.7)</td>
<td>188 (75.2)</td>
<td>0.60 (0.216–1.640)</td>
<td>.31</td>
</tr>
<tr>
<td>GC</td>
<td>48 (18.2)</td>
<td>56 (22.4)</td>
<td>0.47 (0.161–1.359)</td>
<td>.16</td>
</tr>
<tr>
<td>CC</td>
<td>11 (4.1)</td>
<td>6 (2.4)</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>GC+GC</td>
<td>59 (22.3)</td>
<td>62 (24.8)</td>
<td>0.56 (0.206–1.553)</td>
<td>.26</td>
</tr>
<tr>
<td>Allele G</td>
<td>458 (86.7)</td>
<td>432 (86.4)</td>
<td>1.03 (0.719–1.474)</td>
<td>.87</td>
</tr>
<tr>
<td>Allele C</td>
<td>70 (13.3)</td>
<td>68 (13.6)</td>
<td>Ref</td>
<td></td>
</tr>
</tbody>
</table>

N, number of participants.

95% CI=2.114–15.742, P<.001 and the CC genotype of the –174 G/C polymorphism (rs1800795) could be protective because in the genotype CC+GG we identified significant positive association (OR=0.506, 95% CI=0.363–0.869, P<.01).

Discussion

Studies have revealed that interleukins play a key role in both inflammation and the immune response, and are related to various aspects of bronchial asthma. Gene expression of cytokines is regulated by several factors binding to the promoter region. This may result in varied expression, protein concentration and activity, and may affect susceptibility to various inflammatory diseases. Combinations of various gene polymorphisms in interleukins and their receptors result in changes in the interleukin network and its microenvironment. In our study, we investigated the association between 2 promoter polymorphisms of interleukin 6 and bronchial asthma in Slovak patients. We observed a significant association between IL6 –174 G/C polymorphism, bronchial asthma, and a higher prevalence of risk genotype in atopic asthmatic patients. Moreover, we were able to observe a protective combination of polymorphisms.

We observed a significant association between the GG genotype (rs1800795) and G allele and bronchial asthma. The GG genotype of IL-6 –174 G/C was most frequent also in Brazilian asthmatic patients,14 Macedonian children15 and Egyptian children.16 Settin et al. observed positive correlations between polymorphism of the GG genotype of IL-6 –174 and family history and severity of asthma.16 To date, only 1 meta-analysis has studied IL-6 –174 G/C gene polymorphism and bronchial asthma susceptibility in eligible studies. The GG genotype increased risk for asthma, and the CC genotype can be a protective factor against bronchial asthma.17 This meta-analysis supports our results. Different results were observed in Iranian asthmatic populations. Mahdaviani et al. observed significant differences in genotypes of IL-6 genes, though Daneshmandi et al. did not.18,19 However Iranian patients with the GG genotype have elevated concentrations of ILg (not significant).19 In the case of pulmonary function tests, forced expiratory volume in 1 s (FEV1), forced vital capacity (FVC), FEV1/FVC and peak expiratory flow (PEF) did not correlate with IL-6 –174 G/C or –572 G/C genotypes. Similarly, Daneshmandi et al. did not observe changes in pulmonary functions, albeit it with 1 exception–forced expiratory flow between 25% and 75% of vital capacity in IL-6 –174 C vs. G allele differed significantly (49.51±20.4 vs. 65.86±36.42; P=0.045).15 He at al. observed an association between the IL-6 –174 G/C SNP and a rapid decline in FEVI and susceptibility to chronic obstructive pulmonary disease; however, they did not observe an association between polymorphism and serum concentration of IL-6.20 Gruber-Jaworska et al. observed an association between concentration of IL-6 and FEV1 as well as between concentration of IL-6 and FEV1/FVC in 16 asthmatic patients.11 However, they did not observe an association.
between IL-6 concentration and impairment of lung function in COPD patients. A significantly decreased FEV1 was also observed in obese asthmatic patients with increased IL-6 concentration, and concentration of IL-6 was associated with visceral adipose tissue in women with persistent asthma. These conflicting results may be due to ethnic populations, sample size and endotypes of BA and COPD. Genetic predisposition to disease is not consistent between individuals. Different combination of interleukin genotypes may be responsible for different effects on pulmonary functions. One SNP may have no effect, but in combination with another type of SNP or with several SNPs may impair lung function. Interleukin 6 is a multifactorial interleukin, and its production is dependent on different genetic and environmental stimuli. Differences in changes may also be mediated by epigenetic mechanisms. However, various endotypes of asthma exist with a variety of genetic backgrounds, degrees and types of airway inflammation. Significant increase in the GG genotype of IL-6 – 174 was observed in patients with atopic dermatitis, and the authors suggested that production of IL-6 was higher in atopic patients. Our asthmatic patients had higher frequencies of the G allele and the GG genotype compared to healthy subjects and non-atopic asthmatics. A significant association between the IL-6 SNP rs1800797 and the risk of adult-onset asthma, particularly atopic adult asthma, was reported in a South Finland population. These results support our findings.

We did not observe significant changes in IL-6 – 572 G/C (rs1800796) between BA and healthy subjects, although double analysis of SNPs in IL-6 – 174 G/C and IL-6 – 572 G/C shows increased risk of asthma in subjects with combination of GG+GG genotypes (from OR 3.4 to OR 5.8). The GG genotype of IL-6 – 572 G/C may be a promoting factor in combination with IL-6 – 174 G/C polymorphism or with other interleukin SNPs, even though it alone does not increase risk for development of BA. Simultaneous polymorphisms in several interleukins may change IL-6 concentration, thus increasing not only asthma susceptibility but also participating in Th2 response. Interleukin 6 is responsible for T cell differentiation into Th2 and Th17. Interleukin 6 can actively participate in the pathogenesis of bronchial asthma and may be a key modulator of both the overall immune response and the function of non-immune cells. A positive association between polymorphism in interleukin 6 receptor gene and bronchial asthma was observed. Hawkins et al. (2012) found that SNP in IL-6R is associated with lung function in asthmatics, and IL-6R trans-signaling might have a pathogenic role in the airways relating to asthma severity. Moreover, Corvol et al. did not observe a significant association in polymorphism of interleukin 6 with asthma, but showed a significant pharmacogenetics gene–gene interaction between IL-6 and IL-6R genes and bronchodilator drug response in asthma. Because of interleukin 6 signaling through IL-6 receptors, SNPs in both genes and the gene–gene interactions may be responsible for increased inflammation, decreased efficacy of treatment in asthmatic patients and accumulation of damage including oxidative modifications of biomolecules. Oxidative modifications are generated due to increased production of reactive oxygen species (ROS). These are produced during inflammation and are accumulated during repeated inflammatory processes. Furthermore, ROS stimulate production of pro-inflammatory cytokines such as IL-6. We observed increased oxidative damage and association with polymorphisms in antioxidant genes in asthmatic children in our previous studies. Research into treatment of bronchial asthma is currently focused on molecules that are able to reduce the secretion of pro-inflammatory cytokines. Our data need to be confirmed with further studies to increase confidence in our findings.

The study, however, has certain limitations. First, it includes a relatively small number of asthmatic patients (n=264) and healthy children (n=250), which affected the statistical power of the study. Nevertheless, to the best of our knowledge, our series was the largest studied in 2015, and the largest pediatric sample analyzed so far. A second limitation is that we did not analyze IL-6 concentration in BA patients. We consider this to be a pilot study that needs to be expanded.

In conclusion, this study provides evidence of a significant association between functional polymorphisms in interleukin 6 gene and bronchial asthma. These SNPs may affect the clinical parameters of patients. Further studies are needed to replicate these associations in different ethnic populations with larger sample sizes, in order to clarify the biochemical causal mechanism of the effect of interleukin 6 on the origin, development and endotypes of bronchial asthma.

Conflict of Interest
None declared.

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