Association between Gm allotypes and asthma severity from childhood to young middle age

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Immunoglobulin;
Lung function;
Outcome

Summary
Immunoglobulin constant heavy G chain (IGHG) gene polymorphisms are associated with atopy and can be determined by the serum Gm allotypes. We studied whether certain polymorphisms are related to asthma severity and to the extent or intensity of allergic sensitization in asthmatic subjects followed from childhood to young middle age. Fifty-five subjects (28 males) with childhood asthma were all followed-up prospectively on six occasions from a mean age of 9 to 35 years in a study including asthma severity scoring, spirometry, skin prick, and specific serum IgE antibody testing. At the last visit, extended lung function tests and a cold air challenge were performed, and IGHG gene polymorphisms were identified by the alternative serum IgG subclass allotypes, employing ELISA and double immunodiffusion.
The 19 subjects with the homozygous IGHG*bf/*bf genotype (originating from the IGHG3*b and the IGHG1*f alleles, which are in strong linkage disequilibrium), showed significantly higher asthma scores, lower airway function, and greater bronchodilator responses from childhood to adulthood, and in middle age greater airway hyperresponsiveness, compared to the subjects with the IGHG*bf/*ga or IGHG*ga/*ga genotypes. Among the subjects sensitized to animal danders, those with the IGHG*bf/*bf genotype showed the highest specific IgE levels.
In conclusion, IGHG gene polymorphisms were associated with the severity and outcome of childhood asthma, and with the intensity of allergic sensitization.
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Asthma severity and Gm allotypes

Introduction

Asthma is a heterogeneous disorder differing widely in age of onset, severity and outcome. Long-term follow-up studies indicate that growing out of childhood asthma is the exception rather than the rule, and that disease severity in childhood is an important determinant of the outcome.1,2 We have previously reported the course of allergic sensitization, clinical allergy, asthma severity, and airway function in 55 asthma subjects followed-up on six occasions from a mean age of 9–35 years.3–7 We found that allergic sensitization and reported allergies persisted in most subjects, and that the extent of sensitization to perennial allergens was associated with asthma severity and airway hyperresponsiveness.5–7 However, this relationship was not straightforward, suggesting that additional modifying factors are involved.

Gm allotypes (marker for IgG) refer to genetic variations or polymorphisms at loci encoding for the constant heavy chains of IgG (IGHG) and can be identified in serum.8–10 The genetic codes for the heavy constant chains of the IgG and IgG molecules are found on chromosome 14q32.3, with the immunoglobulin heavy constant chain (IGH) genes in the order 5μ, δ, γ3, γ1, α1, γ2, γ4, ε, α2, 3. γ. The IGHG genes display Mendelian inheritance and are expressed randomly by fractionation rates, electrophoretic rates,12 half-life differences,11 but they are separate entities with distinct immunochemical and functional characteristics, such as fractionation rates, electrophoretic rates,12 half-life times,13 and different maturation rate during childhood.14 Table 1 gives the nomenclature used in this paper for the IGHG genes, alleles, and IgG subclass allotypes. Four subsets of IGHG haplotypes (B cells) have been recognized based on the alternative expressions from the IGHG3, IGHG1, and IGHG2 genes, and can be identified via their expressed subclass allotypes.15 The IGHG3 and IGHG1 genes are in absolute linkage disequilibrium (LD): IGHG3*b is linked to IGHG1*f, and IGHG3*g to IGHG1*a.

Previous studies have shown that some Gm allotypes are associated with atopy in children,16 with allergic childhood asthma,17 or with the acquisition of atopic allergy in adults.18 Polymorphisms of IGHG are also known to influence the susceptibility to several diseases, including bacterial and viral infections,19,20 and it is of particular interest that such polymorphisms appear to determine the strength of the antibody response to various antigens.20–22

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Nomenclature and abbreviations used for the IGHG genes, alleles, and IgG subclass allotypes.</th>
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</thead>
<tbody>
<tr>
<td>Gene</td>
<td>Alternative alleles</td>
</tr>
<tr>
<td>---------</td>
<td>---------------------</td>
</tr>
<tr>
<td>IGHG3</td>
<td>γ3</td>
</tr>
<tr>
<td>IGHG1</td>
<td>γ1</td>
</tr>
<tr>
<td>IGHG2</td>
<td>γ2</td>
</tr>
<tr>
<td>IGHG4</td>
<td>γ4</td>
</tr>
</tbody>
</table>

Methods

Subjects

The cohort included 55 subjects (28 males), all ethnic Swedes, with doctor verified childhood asthma. They were randomly recruited to a prospective follow-up asthma study (at a mean age of 9 years) among patients attending a pediatric outpatient asthma clinic. Three or more episodes wheezing were used for the diagnosis of asthma in accordance with Buffum.23 This was the generally used asthma criterion in Sweden during the 1970s. The intentions were to include asthmatic children who would be at least 7 years old at the planned first follow-up (to allow spirometry) and to be half girls and half boys for gender comparison. All subjects attended all six follow-up visits (visit 2–7) at mean ages of 11.5, 13.6, 17.2, 24.3, 30.0, and 34.9 years. Detailed information about the cohort and the findings at all follow-ups has previously been reported.5–7

IGHG genotyping by the IgG alternative subclass allotypes

The IgG subclass allotypes were determined by a sensitive competitive indirect ELISA, measuring both the presence and the serum concentrations of the IgG1f, IgG1a, IgG2n, and IgG3b allotypes and IgG subclass levels, as described in detail elsewhere.11 The sensitivity of the ELISA was 0.0008 g/l for IgG1a, 0.0003 g/l for IgG1f, 0.0006 g/l for IgG2n, and 0.0007 g/l for IgG3b. The heterozygous IgG2n/-n genotype was detected by murine monoclonals anti-G2m(n) 6016-10 clone SH-21 and anti-IgG2 HP 6014 (Sigma) in a double immunodiffusion assay. The IGHG1 alleles and four IGHG haplotypes (B cell variants) were identified, i.e. IGHG*bfn (B1), IGHG*b-f-n (B2), IGHG*gan (B3), and IGHG*ga-n (B4).

Asthma scores

History was taken using a standardized interview questionnaire. Asthma severity (a composite total asthma score, 0–6) was estimated according to the frequency of wheezing episodes (symptom score, 0–3) and the extent of medication for asthma (medication score, 0–3), reported from the year prior to the visit.4 Symptom score 1 denoted occasional wheezing in connection with respiratory tract infections, heavy exposure to allergens, and/or hard physical exercise. Symptom score 2 denoted wheezing up to twice a week and/or after ordinary physical exercise. Symptom score 3 implied wheezing more often than twice a week and/or impairment of daily physical activities. Medication score 1 denoted occasional use of bronchodilator therapy for symptomatic relief, and/or the use of inhaled sodium cromoglycate or steroids for less than 3 months per year.
Medication scores 2 and 3, respectively, denoted the use of bronchodilator therapy when needed and continuous use of one (score 2) or two (score 3) preventive drugs for asthma control.

**Lung function tests**

At visits 2–5, the forced expiratory volume in 1 s (FEV1) was recorded using a wedge bellow spirometer before and after inhalation of salbutamol from a jet nebulizer. In a study performed in the same hospital during the 1970s of 85 healthy subjects aged 7–25 years, the mean (S.D.) increase of FEV1 after salbutamol inhalation was 3.6 (2.3)% in males and 3.5 (2.7)% in females. All spirometric volumes were converted to body temperature, pressure and saturated air (BTPS) conditions, and expressed as percentages of predicted values. Swedish normative data obtained in childen up to 18 years of age or from adults were used where applicable.

At visits 6 and 7 FEV1, vital capacity (VC), and specific airway resistance (sRaw) over five breaths were recorded at rest, 5 and 10 min after a cold dry air hyperventilation challenge (CACH), and after salbutamol inhalation, in a body plethysmograph. The maximum percentage fall in FEV1 after CACH was noted.

Peripheral airway function was assessed at visit 7 using a He (helium) and SF6 (sulfur hexafluoride) single-breath washout performed at rest, approximately 7 min after CACH and 15 min after bronchodilator therapy. The concentration-normalized phase III slopes (SnIII) were computed. A higher SnIII value indicates greater inhomogeneity of ventilation distribution. In the present study only SF6 results are reported.

**Sensitization**

At visit 7 total serum IgE concentrations and specific IgE antibodies to the three most important perennial inhaled allergens in Sweden, which are the danders of cat, dog, and horse, to three pollens (birch, timothy, and mugwort), and to two house dust mites (Dermatofagoides farinae, Dermatofagoides pteronyssinus) were determined using the Phadebas CAP method ("RAST"; Pharmacia Diagnostics, Uppsala, Sweden).

Skin-prick tests (SPT) were performed using a panel of standardized allergen extracts (ALK Copenhagen, Denmark). A weal with a mean diameter (half of the sum of the largest diameter and its midpoint perpendicular) of more than 3 mm was regarded as positive. In the current investigation, the following allergens were included: pollens (birch, hazel, grass, and mugwort), furred animal danders (cat, dog, and horse), and house dust mites (D. farinae and D. pteronyssinus).

**Ethics**

The ethics committee at the Central Hospital in Skövde gave initial approval to the study. During childhood and adolescence the children and their parents gave their informed consent before every follow-up. In adulthood informed consent was received from all subjects.

**Data analysis**

Likelihood ratio (LR) tests were used to test for the Hardy-Weinberg equilibrium (HWE) and to compare diptotype distributions between the asthma cohort and a Caucasian reference population of 587 subjects. Haplotype frequencies for LD estimation were calculated using the Expectation-Maximization (EM) algorithm. Repeated measurements ANOVA was used to investigate genetic effects on bronchodilator response and baseline % predicted FEV1 over all follow-up stations, with the allele count (0, 1, 2) as covariate, while the relationship between the mean total score taken over all follow-up visits and the genotype was tested with linear regression. At the last visit Spearman rank correlation tests were used to assess the relationship to allele counts. Proportions were compared with the Yates corrected χ²-test. Other two group comparisons were made using the Mann–Whitney U-test. A p-value <0.05 was accepted as statistically significant. No corrections for multiple testing were performed since genotypes are correlated with each other due to LD and because the phenotypes assessed by different measures and aspects of asthma are also highly correlated. A Bonferroni correction would therefore be overly conservative. Statistica 6.0 (StatSoft, Tulsa, OK, USA) was used for the statistical analyses.

**Results**

**Genotype and allele distribution**

Six IGHG genotypes were identified with respect to the alternative alleles for IGHG3, IGHG1, and IGHG2. There was a slight deviation from the HWE in the reference population (p = 0.004) with respect to IGHG2 with fewer homozygotes (IGHG2*n/n 10.9%) than expected (22%).

The allele frequencies were similar in the asthma group and the reference population (Table 2). The three genes were all in LD. IGHG3 and IGHG1 were in absolute LD (D = r² = 1), where IGHG3*b was associated with IGHG1*f. IGHG1 and IGHG2 were also in strong LD (D = 0.87, r² = 0.30), where IGHG*b was associated with IGHG*n.

**Table 2** Frequencies of IGHG1 and IGHG2 alleles in the 55 subjects with childhood asthma and in a Caucasian reference population (N = 587; 157 blood donors and 430 healthy children).

<table>
<thead>
<tr>
<th>Alleles</th>
<th>N</th>
<th>%</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGHG1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>*f</td>
<td>69</td>
<td>63</td>
<td>785</td>
<td>67</td>
</tr>
<tr>
<td>*a</td>
<td>41</td>
<td>37</td>
<td>389</td>
<td>33</td>
</tr>
<tr>
<td>IGHG2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>*n</td>
<td>42</td>
<td>38</td>
<td>521</td>
<td>44</td>
</tr>
<tr>
<td>*n</td>
<td>68</td>
<td>62</td>
<td>653</td>
<td>56</td>
</tr>
</tbody>
</table>
Asthma severity and sensitization in young middle age

Correlation analysis showed statistically significant associations between the number of IGHG*bf alleles and several aspects of asthma severity: total asthma scores, bronchial hyperresponsiveness to CACCh, baseline airway resistance, and baseline ventilation inhomogeneity (SF₆ SmIII; all assessed at the last follow-up (Table 3). The relationship between FEV₁/VC (%) and IGHG*bf alleles just failed to reach significance. There were no significant correlations between asthma scores or lung function variables and the number of IGHG2*n alleles (data not given). Total serum-IgE levels or the extent of sensitization, as determined by the number of positive RASTs or SPTs, did not correlate with the number of IGHG*bf alleles (Table 3) or IGHG*n alleles (data not shown).

Asthma course

At visit 7, 5 subjects had a total asthma score of 5 or 6, 10 subjects scored 3 or 4, and 28 had a score of 1 or 2. Asthma was in remission in 12 subjects at visit 7 (21%; 9 males and 3 females) who had a total asthma score of 0. Eight subjects were taking inhaled corticosteroids regularly and four of these also used long-acting beta2 agonists daily.7

Over the six follow-up stations as a whole, total asthma scores were significantly associated with the IGHG*bf allele (p = 0.001; Figure 1). The IGHG*bf allele was also associated with a greater bronchodilator response (p = 0.005) and a lower baseline percentage of predicted FEV₁ (p = 0.024). Total asthma scores or lung function measurement were not significantly associated with the IGHG2 polymorphisms (data not shown).

Asthma severity and sensitization to animal danders

At visit 7, the extent of sensitization, as measured by a positive RAST, to any of the three furred animal danders studied, did not differ significantly between the 19 IGHG*bf homozygotes and the 36 remainders (14/19 vs. 22/36; p = 0.5; Figure 2). All five subject with severe asthma (total asthma scores 5 or 6) were, however, homozygous for the IGHG*bf/*bf genotype and sensitized to at least one animal dander, whilst none of the similarly sensitized subjects with the IGHG*bf/*ga or IGHG*ga/*ga genotypes had severe asthma (p = 0.012; Figure 2).

Subjects with the homozygous IGHG*bf/*bf genotype who were sensitized to any of the three animal danders had higher median serum concentrations of IgE antibodies to these allergens than the similarly sensitized subjects with the IGHG*bf/*ga or IGHG*ga/*ga genotypes: for cat 9.3 kU/l vs. 2.6 kU/l (p = 0.005; N = 11 and N = 21, respectively); for dog 11.9 kU/l vs. 3.0 kU/l (p = 0.035; N = 13 and N = 16, respectively); and for horse 4.1 kU/l vs. 2.4 kU/l (p = 0.170; N = 13 and N = 9, respectively).

Asthma course, gender, and Gm genotypes

Total asthma scores decreased markedly (median reduction 2 score units from visit 2 to visit 7; p = 0.018; Figure 3) over the six follow-up visits among the 10 males who were homozygous for the IGHG*bf/*bf genotype and decreased slightly also among the 18 males with the IGHG*bf/*ga or

### Table 3: Total asthma scores, airway function, sensitization, and total serum-IgE at visit 7 (mean age 34.9 years) in all 55 subjects with respect to IGHG3 and IGHG1 genotypes.

<table>
<thead>
<tr>
<th>Variables</th>
<th>IGHG3 and IGHG1 genotypes</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>*bf/*bf (N = 19)</td>
<td>*bf/*ga (N = 31)</td>
</tr>
<tr>
<td>Total asthma score, median (range)</td>
<td>3 (0–6)</td>
<td>2 (0–4)</td>
</tr>
<tr>
<td>Airway function, mean (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Max fall in FEV₁ after CACCh (%)</td>
<td>21.4 (17.4)</td>
<td>12.0 (10.5)</td>
</tr>
<tr>
<td>Baseline FEV₁ (% pred)</td>
<td>89.6 (12.0)</td>
<td>92.2 (11.4)</td>
</tr>
<tr>
<td>Baseline FEV₁ /VC (%)</td>
<td>73.6 (7.4)</td>
<td>74.9 (7.0)</td>
</tr>
<tr>
<td>Baseline sRaw (kPa s)</td>
<td>1.02 (0.58)</td>
<td>0.77 (0.41)</td>
</tr>
<tr>
<td>Baseline SF₆ SnIII (l⁻¹)</td>
<td>0.255 (0.092)</td>
<td>0.194 (0.078)</td>
</tr>
<tr>
<td>Overall sensitization, median (range)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAST, no. positive tests</td>
<td>4 (0–7)</td>
<td>2 (0–5)</td>
</tr>
<tr>
<td>SPT, no. of positive tests</td>
<td>5 (1–8)</td>
<td>4 (0–7)</td>
</tr>
<tr>
<td>Sensitization to three furred animals tested, median (range)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAST, no. positive tests</td>
<td>3 (0–3)</td>
<td>1 (0–3)</td>
</tr>
<tr>
<td>SPT, no. of positive tests</td>
<td>3 (0–3)</td>
<td>2 (0–3)</td>
</tr>
<tr>
<td>Total S-IgE (kU/l), median (range)</td>
<td>129 (21–4125)</td>
<td>84 (7–860)</td>
</tr>
</tbody>
</table>

The statistical analysis encompasses correlation tests (Rs; Spearman Rho) between the measured variables and the number of IGHG*bf alleles (2, 1, or 0). CACCh = cold air hyperventilation challenge, sRaw = specific airway resistance, SF₆ SnIII = normalized phase III slope for SF₆. For remaining abbreviations, see Methods.
IGHG*bf/*bf genotypes (median reduction 1 score unit; \( p=0.028 \)). By contrast, total asthma scores tended to increase among the females who were homozygous for the IGHG*bf/*ga genotype (median increase 1 score unit; \( p=0.063 \)), and did not change among the female remainders. The difference in score change between males and females was highly significant among those with the IGHG*bf/*bf genotype (\( p<0.001 \)), but not among the remainders (\( p=0.091 \)).

### Discussion

The present study demonstrates a clear association between the IGHG*bf allele and asthma severity in young middle age, judged both clinically and with several tests of airway function. Similar results were recorded all through the follow-up period from childhood. Furthermore, the IGHG*bf allele was related to the intensity of sensitization to perennial allergens. The IGHG*bf alleles were, however, not overrepresented in the cohort compared to a reference population, indicating that they are not linked to the risk of acquiring asthma.

To our knowledge, there are no previously published studies on Gm allotypes and the course and outcome of childhood asthma. At the last follow-up, the highest asthma scores, the most pronounced airway hyperresponsiveness, and the lowest baseline central (sRaw) or peripheral (SF6 SnIII) airway function were found among the subjects with the homozygous IGHG*bf/*bf genotype. The subjects lacking these alleles had the lowest asthma scores, were least reactive to cold air challenge and had the best baseline airway function, whilst the heterozygotes showed intermediate results. Over the whole 26-year follow-up period, the IGHG*bf/*bf genotype was associated with the most severe asthma judged both from clinical scores and lung function findings. The extent of allergic sensitization or total serum IgE did not show a clear association with the IGHG*bf alleles. Interestingly, severe asthma was found only in subjects with the IGHG*bf/*bf genotype who were sensitized to at least one animal dander. Furthermore, the intensity of sensitization to furred animal allergens was higher in the sensitized subjects who had the IGHG*bf/*bf genotype than in the sensitized remainders.

It is well known that there are differences in asthma prevalence and airway behavior between males and females over lifetime.\(^2,10\) In the present study, the difference in total asthma scores between the IGHG*bf/*bf genotype and the remainders was seen in both sexes over the whole

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**Figure 1** Mean total asthma scores, mean percentage increase in FEV\(_1\) after bronchodilation (reversibility %), and mean baseline FEV\(_1\) (% predicted) in all 55 subjects over visits 2–7 with respect to IGHG genotypes: IGHG*bf/*bf (N = 19) (black filled circles), IGHG*bf/*ga (N = 31) (gray filled circles), and IGHG*ga/*ga (N = 5) (open circles). (p-values refer to comparisons between the three groups over the follow-up as a whole.)

**Figure 2** Asthma severity (total asthma scores) distribution at visit 7 in relation to the extent (0–3) of sensitization (limit for positive RAST > 0.70 kU/l) to three furred animals danders (cat, dog, and horse) among the 19 subjects homozygous for the IGHG*bf/*bf genotype, and among the remainders (31 IGHG*bf/*ga and 5 IGHG*ga/*ga subjects).

**Figure 3** Mean total asthma scores over visits 2 to 7 for male and female subjects with the IGHG*bf/*bf genotype (circles; \( N = 19 \)) and for male and female subjects with the IGHG*bf/*ga (\( N = 31 \)) or the IGHG*ga/*ga genotypes (\( N = 5 \)) (triangles).
follow-up. The previously reported greater improvement of asthma severity among the males vs. the females in this cohort was most pronounced among those with the IGHG*bf/*bf genotype, where the males had the largest room for improvement.

The study included relatively few patients, but they all attended all follow-up visits over a period of 26 years and their asthma was carefully characterized with respect to clinical, allergological, and physiological features. The follow-up covered a period of life when major changes occur in terms of growth, maturation, and living conditions. Nevertheless, distinct differences in clinical asthma severity and lung function were found between the different IGHG3/IGHG1 genotypes over the whole follow-up period. Furthermore, our finding of an allele dose-response with respect to airway hyperresponsiveness and lung function is characteristic for a gene influence. However, if the initial difference in asthma severity between the genotypes had occurred by chance, not involving any causal relationship, then it would probably persist over the follow-up. There is therefore a need to assess these associations in other asthma populations.

There was no significant relationship between the number of IGHG2*n alleles and asthma severity or allergic sensitization. In a previous study in childhood asthma, an association was found between the IGHG*bfn/*bfn genotype and allergic asthma. In another study, an overrepresentation of the IGHG*bfn allele was found in laboratory technicians developing allergy to furred animals. A recent study of subjects participating in the International Study of Asthma and Allergy in Children (ISAAC) showed an association between the IGHG*bfn allele and the occurrence of allergic sensitization, family history of atopy, and clinical allergy. As expected in a pediatric asthma population, the great majority of the subjects in the present asthma cohort (90%) were sensitized to any allergen. Therefore, the influence of any polymorphisms on adopting allergic sensitization could not be assessed.

The study patients were recruited randomly among Swedish asthmatic school children born during the 1960s and referred from primary care physicians to a pediatric outpatient asthma clinic in a general hospital in the mid-1970s. This was prior to the “asthma epidemic”, which is generally regarded to be the result of a modern Western life style. As asthma is thought to result from the interaction between several genes and environment, it can be speculated that the gene interaction with the altered environment and life style of today promotes asthma development also in other genotypes than those associated with acquiring asthma in the 1960s. It therefore remains to be seen if asthma severity and long-term asthma outcome in school children born more recently and also in those with non-Caucasian origin are similarly associated with IGHG polymorphisms.

Over the follow-up period, bronchodilator response was greater in the 19 subjects with the homozygous IGHG*bf/*bf genotype than in the remaining 36 subjects, indicating that these alleles are related to bronchial hyperresponsiveness. At the last follow-up visit, tests of large and small airway function showed that the whole airway tree was more severely affected in the subjects with homozygous IGHG*bf/*bf genotype. A clear relationship has previously been shown between the degree of airway responsiveness in asthma and the intensity of airway inflammation, giving indirect evidence of greater airway inflammation among the subjects with IGHG*bf/*bf genotype during the whole follow-up period. The greater intensity of allergic sensitization to perennial allergens in this subgroup lends support to this notion.

To conclude, the present study shows a clear and consistent association between IGHG gene polymorphisms, identified by the alternative serum IgG subclass allotypes, and asthma severity from childhood to young middle age, and that these polymorphisms are related to the intensity of allergic sensitization to relevant perennial allergens.

Conflicts of interest

None of the authors has any interests of conflict to declare with respect to this paper.

Acknowledgment

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References

13. Oxelius V-A, Eibl MM. Different Gm allotype levels in human intravenous immunoglobulin (IVIG) preparations, survival of


17. Oxelius VA, Hultquist C, Husby S. Gm allotypes as indicators of non-atopic and atopic bronchial asthma. Int Arch Allergy Immunol 1993;101:66–71.


