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Development of Allergy to Laboratory Animals Is Associated with Particular Gm and HLA Genes

Abstract

To find out whether IgG genes are involved in atopy we studied 26 of 101 laboratory technicians who had developed laboratory animal allergy (LAA). The genes for the constant region of the heavy chains of IgG subclasses were analyzed by serum Gm allotypes, representing products on allelic level of the IGHCG1, IGHCG2 and IGHCG3 on chromosome 14q32. There was a significantly increased frequency of the Gm(f,f;n,n;b,b) genotype (57.7 instead of 22.3%, $p < 0.001$) representing IgG1, IgG2 and IgG3 molecules and in particular increased frequency of Gm genotypes with the homozygous expression of G2m(n,n) (69.2 instead of 27.4%, $p < 0.001$) and of the Gm(f,n,b) haplotype (75 instead of 44.8%, $p < 0.001$) compared to a normal Caucasian population. An increased HLA-DR4 content of the LAA group (61.5 instead of 33.7%, $p < 0.01$) was further investigated for Gm allotypes. Among 16 HLA-DR4 LAA individuals, the Gm(f,f;n,n;b,b) genotype (56.3 instead of 22.3%, $p < 0.01$) and the Gm genotypes with the homozygous expression G2m(n,n) (62.6 instead of 27.4%, $p < 0.01$) dominated. However, the HLA-DR4 frequency among Gm(f,f;n,n;b,b) of LAA patients did not deviate from the frequency of healthy individuals of the same Gm genotype. The increased frequency of HLA-DR4 antigen in LAA patients might be due to its association to the Gm(f,f;n,n;b,b) genotype. This study supports the following concept: the susceptibility of developing LAA is associated with Gm allotypes G1m(f) expressed from IGHCG1, G2m(n) from IGHCG2 and G3m(b) from IGHCG3 on both alleles situated close to IGHCE on chromosome 14q32. The association of LAA to Gm allotypes [Gm(f,f;n,n;b,b)] expressed from chromosome 14q32 and of HLA class II antigens (HLA-DR4) expressed from chromosome 6p21.3 further confirms the polygenic inheritance of the immune response in atopy.

Key Words

Gm allotypes

HLA class II antigens

Atopy

Laboratory animal allergy

Introduction

The genes for the constant region of the heavy chains of IgE, IgA and IgG subclasses are closely packed in the telomeric region of chromosome 14. The products of genes for the constant part of the heavy chains of IgG subclasses can

be investigated in serum by Gm allotypes [1], which express the allelic variation of IgG subclass molecules with Mendelian inheritance. The Gm allotypes originate from epitope differences of the constant region of the heavy chain of the IgG1, IgG2 and IgG3 subclasses. The IGHCG1, IGHCG2 and IGHCG3 can be studied by the alternative, allelic Gm

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Table 1. IgE and IgG subclass levels of the atopic and the control technicians and IgG subclass levels of 157 healthy blood donors (mean $\pm$ SD)

	n	IgE, KU/l	IgG1, g/l	IgG2, g/l	IgG3 g/l	IgG4, g/l
Atopic technicians	26	64.6 $\pm$ 102.4*	6.72 $\pm$ 1.68	3.56 $\pm$ 0.80	0.65 $\pm$ 0.22	0.44 $\pm$ 0.25
Control technicians	25	24.1 $\pm$ 21.2	6.69 $\pm$ 1.41	3.39 $\pm$ 0.96	0.63 $\pm$ 0.27	0.38 $\pm$ 0.42
Blood donors	157	ND	6.81 $\pm$ 1.23	3.56 $\pm$ 1.02	0.67 $\pm$ 0.23	0.42 $\pm$ 0.32

* $p < 0.05$. ND = Not done.

markers for IGHCG1 by G1m(a) and G1m(f), for IGHCG2 by G2m(n) and G2m(") and for IGHCG3 by G3m(g) and G3m(b)[1].

Atopic children predominantly expressed G1m(f) for the IGHCG1 gene, G2m(n) for the IGHCG2 and G3m(b) for IGHCG3, namely the homozygous Gm(f,f;n,n;b,b) genotype [2]. In addition, an association between this Gm(f,f;n,n;b,b) genotype of atopic children and significantly increased serum IgG4 and IgE levels has been observed [3]. Increased IgG4 has earlier been noted in patients with the most severe atopic disease [4]. We therefore suggested the homozygous Gm(f,f;n,n;b,b) phenotype as a marker for severe atopy [3].

Complex genetic and environmental factors have been identified which contribute to the manifestation of atopy. There is evidence that inheritance of the immune response in atopy is polygenic. The association of HLA Dw2 antigen on chromosome 6, to rag weed allergy was early documented [5, 6]. Recently, chromosome 11q13 [7] and gene locus for the β -unit of the high-affinity IgE receptor [8] were found to be associated with atopy, as well as chromosome 5q31.1 with the genes coding for IL-4 [9].

Our aim was to assess whether the Gm allotypes which express IGHCG1, IGHCG2 and IGHCG3 with close relationship to IGHCE on chromosome 14 were involved in the development of laboratory animal allergy (LAA). The study population was an outbred highly polymorphic population of laboratory technicians who had developed atopic symptoms on laboratory animal exposure [10]. The study population was earlier reported with increased frequency of particular HLA antigens [11]. The relationship between Gm allotype and HLA antigens was also investigated.

Subjects and Methods

Subjects

Of 101 Caucasians who are currently employed laboratory technicians occupationally exposed to laboratory animals at 25 research laboratories at the Lund University, 26 were selected with symptoms indicating LAA. The study group and an age sex-matched control group of 25 healthy laboratory technicians, have been described in detail [10]. All had rhinitis and 11 also asthma and were skin-prick-test-positive for animal allergens. A history of allergy in any relative was statistically significantly associated with LAA. The association was particularly close in animal-test-positive subjects with LAA asthma. The LAA group showed an increase in skin prick positivity. Skin prick tests were performed with a standard battery of 13 common environmental allergens and with six laboratory animal species (rat, mouse, guinea pig, cat, rabbit and hamster). The scored exposure to laboratory animals showed similar levels in the different groups. The IgE levels of the LAA group were significantly increased compared to a control group (table 1). We have previously investigated predisposing factors, e.g. exposure to domestic animals, smoking habits, passive exposure to tobacco smoke and chemicals and HLA antigens in a follow-up study 5 years later [10–12].

Methods

Gm Determination. Gm allotypes were determined by the classical hemagglutination inhibition method using the microtiter system [1, 13]. The reagents used were for G1m(a): anti-Gm 2400041 and anti-D 2401455, for G3m(g): anti-Gm 2400445 and anti-D 2401859 and for G3m(b): anti-Gm 2400546 and anti-D 2401960 (Janssen Biochimica, Beerse, Belgium).

G1m(f) and G2m(n) determinations were done by radial immunodiffusion [14] with murine monoclonal antisera specific to these allotypes: anti-G1m(f) 6006–10 clone SG-16 and anti-G2m(n) 6016–10 clone SH-21 (Sigma, St Louis, Mo., USA) published previously [2, 3]. For the determination of homozygosity and heterozygosity of G2m(n), a double diffusion assay [15] was used with the monoclonal reagents: anti-G2m(n) 6016–10 clone SH 21 and anti-IgG2 HP 6014 (Sigma). The frequency figures of Gm markers were compared with a normal Swedish population consisting of 157 healthy blood donors 96 males and 61 females [16]. The results were given as frequencies of the whole genotype representing the alternative Gm alleles for IgG1, IgG2 and IgG3 (tables 2, 3) but also as the frequencies of possible Gm haplotypes (table 4).

IgG Subclass Determination. Serum IgG1, IgG2, IgG3 and IgG4 were determined with radial immunodiffusion [14] using polyclonal

rabbit antisera as described before and compared to values of 157 healthy blood donors reported earlier [16].

HLA-Antigen Determination. HLA antigen frequencies from an earlier publication were used [11]. Figures were compared to frequencies found for a Caucasian healthy population (95 of the 157) also investigated for Gm allotypes [16].

Statistical Methods. The Gm allotype frequencies of the study groups, compared to the normal Swedish population [16] were calculated by the χ^2 -test with Yates correction. Means $\pm$ SD of IgE and the four different IgG subclasses of the atopic and the control group were compared by the Z test.

Results

Analyses of Serum Gm Allotypes as Markers for IGHCG1, IGHCG2 and IGHCG3

Twenty-six of 101 laboratory technicians with LAA employed at the University of Lund were investigated. On exposure they had developed symptoms of bronchial asthma and/or allergic rhinoconjunctivitis. Their atopic constitution was verified by increased IgE and positive skin prick tests. Among LAA subjects, the Gm allotypes deviated compared to a normal Swedish population (table 2: Gm allotypes). There was a significantly increased number of patients with the Gm(f,f;n,n;b,b) genotype (57.7 instead of 22.3%, $p < 0.001$). This Gm genotype represented homozygous expression of G1m(f,f) from IGHCG1, of G2m(n,n) from IGHCG2 and of G3m(b,b) from IGHCG3. The total number of Gm genotypes expressing G2m(n,n) from IGHCG2 was also significantly increased (69.2 instead of 27.4%, $p < 0.001$). In the same way the number of LAA patients with Gm genotypes expressing the alternative G1m(a,a) from IGHCG1, G2m(","") from IGHCG2 and G3m(g,g) from IGHCG3 were significantly decreased (table 2). The increased frequency of the Gm(f,n,b) haplotype was highly significant, compared to the 25 healthy controls of the 101 under study (table 4).

Table 2. Frequencies of Gm genotypes in 26 Caucasians with LAA : patients with selected HLA class I and class II antigens, compared to the normal Swedish population.

	Symptom group (26)	HLA B15 (10)	HLA Cw3 (12)	HLA DR4 (16)	Swedish population (157)
A/					
<i>Gm allotypes</i>					
a f n " g b					
- + + - - +	57.7***	30	50	56.3**	22.3
- + + + - +	3.8	10	8.3	6	20.4
- + - + - +	0	0	0	0	7.0
+ + + - + +	11.5	10	8.3	6.3	3.9
+ + + + + +	19.2	40	25	19	19.1
+ + - + + +	7.7	10	8.3	12.5	12.1
+ - + - + -	0	0	0	0	0
+ - + + + -	0	0	0	0	1.3
+ - - + + -	0*	0	0	0	14.0
B/					
<i>G2m allotypes</i>					
+ -	69.2***	40	58.3	62.6**	27.4
+ +	23.1	50	33.3	25.3	39.4
- +	7.7**	10	8.3	12.5	33.1
C/					
<i>G1m (G3m) allotypes</i>					
- + - +	61.5	40	58.3	62.6	49.7
+ + + +	38.5	60	41.6	37.8	35.0
+ - + -	0*	0	0	0	15.2

*** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$, vs. the normal Swedish population.

Table 3. Frequencies of HLA antigens in the atopic group (A) with LAA (n = 26) and a Caucasian control healthy population of 95 blood donors (C), especially those with the homozygous Gm(f,f;n,n;b,b) genotype

	Atopic group (A) 26		Control population (C) 95		Gm(f,f;n,n;b,b) of (A) 15		Gm(f,f;n,n;b,b) of (C) 22	
	n	%	n	%	n	%	n	%
HLA-B15	10	38.5	22	23.2	3	20	8	36.4
HLA-Cw3	12	46.1	43	45.3	6	40	12	54.5
HLA-DR4	16	61.5**	32	33.7	9	60	8	36.4

** $p < 0.01$, vs. controls.

Table 4. The Gm haplotype frequencies (%) of 26 LAA technicians and of 25 healthy technicians compared to 157 blood donors

Haplotype	LAA technicians 26×2		Healthy technicians 25×2		Blood donors 157×2	
	%	n	%	n	%	n
a,n,g	5.8	3	16	8	0.9	10
a'',g	13.5	7*	26	13	31.4	93
f,n,b	75.0	39***	42	21	44.8	138
f'',b	5.8	3**	16	8	22.9	73

***p<0.001, **p<0.01, *p<0.05, vs. blood donors.

Gm Allotypes in Subgroups of LAA Patients with Different HLA Class I and Class II Antigens

Gm allotypes deviated in a subgroup of LAA patients expressing HLA-DR4 antigen. In the 16 patients with HLA-DR4, there was a significantly increased number of the homozygous Gm(f,f;n,n;b,b) genotype and also of genotypes with homozygous expression of G2m(n,n) on IGHG2. In the HLA-DR4 group the dominance of Gm(f,f;n,n;b,b) was 56.3% (instead of 22.3%, $p<0.01$) and of G2m(n,n) genotypes 62.6% (instead of 27.4%, $p<0.01$) respectively (table 2). There was no deviation of Gm allotypes in the HLA class I, HLA-B15 and HLA-Cw3 subgroups of LAA patients tested (table 2).

HLA Class I and Class II Antigens in LAA Patients with Special Reference to the Gm(f,f;n,n;b,b) Phenotype

Sixteen of the technicians who had developed LAA were also carriers of the HLA class II antigen HLA-DR4 which was significantly increased (61.5 instead of 33.7%, $p<0.01$; table 3). No significant difference in DR4 frequency could be shown when examining the genotype Gm(f,f;n,n;b,b) of the LAA subjects compared to Gm(f,f;n,n;b,b) of healthy controls (table 3).

Serum IgE and IgG Subclass Levels

IgE levels of the technicians with LLA were increased in comparison with the control group of laboratory technicians, but IgG subclass levels did not differ significantly compared with the control group of the laboratory technicians or the healthy Caucasian control population (table 1).

Discussion

The susceptibility to develop LAA is associated with the expression from IGHCG1, IGHCG2 and IGHCG3 situated close to IGHCE on chromosome 14q32. The homozygous Gm(f,f;n,n;b,b) genotype dominated significantly as well as genotypes with G2m(n,n) from IGHCG2. The Gm(f,n,b) haplotype was highly frequent. It appears that the switch to IgE is more favored when the genes upstream consist of (in order) the gene G3m(b) from IGHCG3, G1m(f) from IGHCG1 and G2m(n) from IGHCG2. The skew distribution might also be due to a linkage disequilibrium between the IgG subclass genes, expressed by Gm(f,n,b) and a high responder IgE gene. Linkage disequilibrium including G1m(f) and G3m(b) is a rule for Caucasians, but in atopic subjects an additional linkage disequilibrium including G2m(n) and the high responder IgE gene locus might be suggested. The findings also focus new interest on IgG molecules in atopy as the Gm(f,f;n,n;b,b) indicate restricted variability of the heavy chain of the IgG subclasses in LAA individuals with the homozygous expression of G1m(f,f) of IgG1 molecules, G2m(n,n) of IgG2 molecules and G3m(b,b) of IgG3 molecules.

The predominance of the Gm(f,f;n,n;b,b) genotype has earlier been found in atopic children [2]. The influence of Gm allotype genes and gene dosages on IgE levels has also been reported [3]. The Gm(f,f;n,n;b,b) genotype correlated to the highest IgE and IgG4 levels, known to be associated with the most severe form of atopy [4]. In LAA individuals, the Gm(f,f;n,n;b,b) phenotype was associated with sensitization and symptoms on exposure to animal allergens. In the patients under study the predominance of the Gm(f,f;n,n;b,b) was found together with significantly increased IgE levels, however, but not increased IgG subclass levels, compared to the control technician group. In atopic children with serum IgE > 600 KU/l, the Gm(f,f;n,n;b,b) genotype was found with increased IgG1, IgG2 and IgG4. In our experience high IgG4 levels are seen more often in atopic children than in adults.

The study group of 26 technicians with LAA has been well defined and was investigated also in a follow-up study [10, 12]. They fulfilled the criteria of an outbred highly polymorphic group, selected among 101 individuals, on clinical and diagnostic grounds.

The possible HLA antigen association was earlier reported for this LAA group with increased frequency of both HLA class I, (HLA-B15) and class II antigens (HLA-DR4) [11]. In the present investigation, we could confirm an increased frequency of HLA-DR4 in the LAA group, in whom also the Gm(f,f;n,n;b,b) and homozygosity G2m

(n,n) from IGHCG2 dominated. However, the HLA-DR4 frequency in the Gm(f,f;n,n;b,b) of LAA was not different from that in the Gm(f,f;n,n;b,b) of controls. This might indicate that the increased frequency of HLA-DR4 in LAA actually was due to increased frequency of HLA-DR in Gm(f,f;n,n;b,b) individuals.

Both qualitative and quantitative IgG and IgE responses to ragweed allergen Ra5 were observed to be strongly associated to HLA-Dw2 [5]. After artificial immunization with ragweed antigens, the specific IgG response was significantly associated to HLA-Dw2 [6]. These HLA-Dw2-Ra5 associations were found to be the strongest HLA associations observed with a defined immune response in a polymorphic human population. But because of the variable expression of the immune response they suggested involvement of further genetic loci [6].

The association between Gm allotypes and HLA antigens reflects the complexity of the immune response in atopy, as genes coding for immunoglobulins and HLA specificities are active throughout the development of the immune response. HLA antigens are important for antigen presentation, antigen handling and interaction with T cells. Both HLA and Gm allotypes are related to antigen handling and may affect the rate of degradation of the antigens by macrophages. This was shown in individuals with the HLA-DR3 and the Gm(f,n,b) haplotype who slowly degraded sheep erythrocyte antigens [17]. In the murine system, such slow antigen degradation is associated with high antibody production. As seen in atopic children, the genotype Gm(f,f;n,n;b,b) is associated with increased IgE, IgG1, IgG2 and IgG4 levels [3].

The Gm allotype-HLA antigen association is known from other autoimmune disorders. HLA-DR4 has been found to be associated to G3m(b) but also HLA-DR3 to G1m(x) in type I diabetes mellitus [18]. Interactive effects of Gm and HLA on rheumatoid arthritis were confirmed with combined involvement of G1m(x) with HLA-DR4 in patients with collagen antibodies and Gm(z,a,f;n,g,b) with HLA-DR3 and DR7 in those without antibodies [19]. Different Gm allotypes influence different clinical forms and prognosis of juvenile chronic arthritis [20]. However, none of the HLA associations or Gm associations with disease have been shown to be absolute, suggesting that possession of particular Gm allotypes and tissue types are only some of several etiological factors involved.

The immune response in most LAA individuals involves an IgG with special characteristics. The IgG2 molecules were found as homozygous expression of G2m(n,n) allotypes reported to be associated with a better antibody response to bacterial infections, especially to polysaccha-

ride antigens [21–23]. The homozygous expression of IgG1 molecules as G1m(f,f) and of IgG3 molecules as G3m(b,b) further indicate a restricted heterogeneity within the different IgG subclasses. The effect of this is not known. In non-atopic asthmatic children, who are often prone to infection, the Gm phenotype with the alternative homozygous Gm allotypes G1m(a,a) from IGHCG1, G2m(",) from IGHCG2 and G3m(g,g) from IGHCG3 was reported [24]. The G2m(",) has earlier been suggested as a marker for non-atopic bronchial asthma. The homozygous G2m(",) from IGHCG2 is normally associated with low IgG2 and IgG3 levels and with IgG subclass deficiency.

Genetic linkage has been reported between generalized atopic responses and a locus on human chromosome 11q13 [7]. A significant feature of this linkage was the maternal inheritance displayed by this locus [25]. Recently, a mutation of the β -unit of the high-affinity IgE receptor was suggested as the atopy-causing locus on chromosome 11q13 [8]. A common variant Ile181Leu within the fourth transmembrane domain of the β -subunit of the high-affinity IgE receptor, was identified. Leu181 showed a significant association with positive IgE responses [8]. This receptor exerts a regulatory effect on IgE production through IL4 production by mast cells [26]. IL-4 is a critical mediator of B cell switching and IgE synthesis and also IgG4 synthesis. Recent evidence indicates that markers around the IL-4 locus on chromosome 5q31.1 are linked to a gene controlling the IgE levels. The pathway by which allergens trigger IgE production and subsequent mast cell activation suggest that several loci are likely to play a role in atopy. Additionally, characteristic Gm allotypes on chromosome 14q32 are reported in LAA individuals together with characteristic HLA class II antigens on chromosome 6p21.3, which further confirm the polygenic inheritance of the immune response in atopy.

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