J Clin Immunol (2010) 30:138–143
DOI 10.1007/s10875-009-9336-2

IgA Deficiency and the MHC: Assessment of Relative Risk and Microheterogeneity Within the HLA A1 B8, DR3 (8.1) Haplotype

Javad Mohammadi · Ryan Ramanujam · Sara Jarefors · Nima Rezaei · Asghar Aghamohammadi · Peter K. Gregersen · Lennart Hammarström

Received: 29 July 2009 / Accepted: 24 September 2009 / Published online: 16 October 2009
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Abstract
Introduction Selective IgA deficiency (IgAD; serum IgA concentration of <0.07 g/l) is the most common primary immunodeficiency in Caucasians with an estimated prevalence of 1/600. The frequency of the extended major histocompatibility complex haplotype HLA A1, B8, DR3, DQ2 (the "8.1" haplotype)is increased among patients with IgAD.
Materials and Methods We carried out a direct measurement of the relative risk of homozygosity of the 8.1 haplotype for IgA deficiency in a population-based sample of 117 B8, DR3 homozygous individuals.
Results and Discussion IgA deficiency was found to be present in 2 of 117 (1.7%) of these subjects, a figure that is concordant with estimates of relative risk from large case–control studies in the Swedish population. These data are consistent with a multiplicative model for the 8.1 haplotype contribution to IgA deficiency and contrasts with prior studies, suggesting a much higher risk for 8.1 homozygosity. Using a dense single nucleotide polymorphism marker analysis of the MHC region in HLA B8, DR3, DQ2 homozygous individuals, we did not observe consistent differences between cases (n=26) and controls (n=24). Overall, our results do not support the hypothesis that IgA deficiency is associated with a distinct subgroup of 8.1 related haplotypes, but rather indicate that risk is conferred by the common 8.1 haplotype acting in multiplicative manner.

Keywords HLA · immunogenetics · immunodeficiency · IgA deficiency

Electronic supplementary material The online version of this article (doi:10.1007/s10875-009-9336-2) contains supplementary material, which is available to authorized users.

J. Mohammadi · R. Ramanujam · S. Jarefors · L. Hammarström (✉)
Division of Clinical Immunology,
Department of Laboratory Medicine, Karolinska Institutet at Karolinska University Hospital Huddinge,
141 86 Stockholm, Sweden
e-mail: Lennart.Hammarstrom@ki.se

N. Rezaei · A. Aghamohammadi
Children's Medical Centre, Growth and Development Research Center, Pediatrics Center of Excellence, Children's Medical Centre, Tehran University of Medical Sciences,
Tehran, Iran

P. K. Gregersen
The Feinstein Institute for Medical Research,
Manhasset, NY, USA

Introduction

Selective IgA deficiency (IgAD; serum IgA concentration of <0.07 g/l) is the most common primary immunodeficiency in Caucasians with an estimated prevalence of 1 in 600 [1]. Many of these individuals have no apparent disease, while some suffer from recurrent infections at mucosal sites, allergies, and autoimmune diseases (for review, see [1, 2]). A markedly differing population prevalence among ethnic groups [3, 4], familial clustering of the disorder [5], a predominant inheritance pattern in multiple-case families compatible with autosomal dominant transmission and a high relative risk for siblings [6] suggest that currently unidentified genetic factors are responsible for development of the disorder [7].

Although IgAD is likely to be a polygenic disorder, a major component of the predisposing factor(s) is located within the HLA region. An increased frequency of the HLA B8, DR3, DQ2 alleles and the corresponding haplotype has previously been found in patients with selective IgAD [8, 9] and increased frequencies of several other extended haplotypes, including DR7, DQ2 and DR1, DQ5 have also

been reported [10]. The location of the susceptibility gene (s) within this region, however, remains controversial [9, 11]. Previous studies have suggested that two separate loci, located in the MCH class II and class III region, respectively, carry susceptibility genes for the development of IgAD [12, 13]. Thus, a predisposing locus on the HLA DR1 and DR7 carrying haplotypes, IGAD1, has been suggested to map to the class II region, whereas the susceptibility locus on the HLA DR3 haplotype has been suggested to map to the telomeric end of the class III region [14].

IgAD has been previously shown to be overrepresented in patients with autoimmune diseases such as rheumatoid arthritis [15, 16], systemic lupus erythematosus (SLE) [17], and juvenile diabetes mellitus [18]. The coexistence of autoimmune disease and IgAD may arise from their common association with polymorphisms/mutations in genes within the ancestral HLA A1, B8, DR3, DQ2 haplotype.

Strikingly, previously published studies indicate a 13% prevalence of IgAD in individuals who are homozygous for the HLA B8, DR3 haplotype [19–21], with extremely high relative risks (RR=77.8). This high relative risk of the homozygous genotype suggests either a strong genetic interaction or the possibility that highly penetrant subgroups of the 8.1 haplotype may exist. However, these data are based on relatively few individuals, and therefore we sought to re-evaluate the role of homozygosity of the HLA B8, DR3, DQ2 haplotype for the development of IgAD.

Materials and Methods

Subjects

Three groups of unrelated Caucasian subjects (117 individuals), homozygous for the entire, or part of, the HLA A1, B8, DR3, DQ2 haplotype were studied: 78 cases from the Swedish volunteer bone marrow donor registry (www.tobiasregistret.se), 30 cases from routine tissue typing of relatives of patients evaluated prior to transplantation, and nine population-based controls from the Rheumatology Unit, Department of Medicine at the Karolinska University Hospital. It is important to emphasize that all subjects were chosen solely on the basis of MHC haplotypes and were not included in the study because of prior knowledge of immunoglobulin levels. Four hundred and twenty-one unrelated Swedish IgAD patients from the immunodeficiency unit at the Karolinska University Hospital Huddinge were also included in the study in order to determine the frequency of the HLA B8, DR3, DQ2 haplotype in affected individuals. Ethical permission was obtained from The Research Committee of the Karolinska Institute for use of the samples collected in the study.

Serum Immunoglobulin Levels

Serum levels of IgG, IgA, and IgM were measured by nephelometry. A sample was considered IgAD if the concentration of IgA was below 0.07 g/l (the diagnostic criteria for IgAD are available at http://www.esid.org/home.php).

HLA Typing

Samples were genotyped at the HLA A, B, DR and DQ loci using serology or PCR-SSP [22]. The kits used in this study included the HLA B low resolution (L21, M26, J82, N80, N02, R56, X13, X82) and the HLA DQ-DR SSP Combi Tray (K88, R60, V95, M01, M84) from Olerup SSP AB, Saltsjöbaden, Sweden.

SNP Analysis

Two separate single nucleotide polymorphism (SNP) maps were constructed using genotyping data. The first map used 1,116 SNPs across the MHC from upstream of HLA A to downstream of HLA DP. These SNPs were extracted from an Illumina custom array panel described previously [23]. An additional 896 SNPs across the same region were typed using the Illumina HumanHap300 (317 K) genotyping BeadChip. Merging the data sets and removing duplicate SNPs left a total of 1,718 unique SNPs across the MHC. Swedish IgAD patients, homozygous for the HLA B8, DR3, DQ2 haplotype (n=18), were compared to population-based controls (n=9) with normal IgA levels who were homozygous for this haplotype.

The second SNP map consisted of 3,874 SNPs across the same region using the Illumina Human610-Quad (620 K) genotyping BeadChip array. This SNP map included additional HLA B8, DR3, DQ2 homozygous Swedish IgAD patients (n=8) and IgA sufficient donors from the Swedish volunteer bone marrow registry (n=15).

The SNP maps were constructed by examining the genotypes of all individuals at all SNPs and using PERL scripts to create a genotype file, in which the genotype aa is represented by 0, Aa by 1, and AA by 2. A graphical map was then assembled and color-coded by genotype to elucidate the differences present between IgAD patients and controls with the given haplotype.

Results

Calculating Relative Risk of IgAD Among HLA B8, DR3 Homozygous Individuals

The results of HLA typing for individuals homozygous for the B8, DR3 haplotype are given in Table I. No DNA

Table I HLA Typing Results in Swedish Individuals Homozygous for the HLA B8, DR3 Haplotype

Haplotype				Number of samples			Total
A1	B8	DR3	DQ2[a]	Volunteer registry	Transplantation donors	Population control samples	
•	•	•	•	41	1	9	51
•	•	•		19	17	0	36
	•	•	•	17[b]	1[c]	0	18
	•	•		1[b]	11[c]	0	12
			Total	78	30	9	117

Only samples that could be typed at HLA B and HLA DR and were homozygous for B8, DR3 were included in the study

[a] All samples without information for DQ2 could not be typed at this locus. Due to the strong LD between the alleles in the HLA B8, DR3, DQ2 extended haplotype and based on data on our Swedish controls (n=672), our Swedish IgAD patients (n=429) [26], and Swedish MG patients (n=580), no individuals homozygous for the HLA B8, DR3 but negative for the DQ2 have been observed

[b] Of these 18 samples, 12 could not be typed at A1, four were heterozygous for A1, and two were not A1

[c] Of these 12 samples, 10 were heterozygous for A1, and two were not A1

samples were available to perform supplemental HLA typing for the missing HLA A (12 individuals) and DQ (48 individuals) loci (Table I). However, due to the strong linkage disequilibrium (LD) between the alleles in the extended HLA B8, DR3, DQ2 haplotype [24, 25], the vast majority (potentially all) of the individuals included in present study would be expected to be homozygous for the HLA DQ2 allele, whereas, based on our current analysis of 105 individuals with complete HLA A, B, DR typing results, only 81.9% would be expected to be A1 homozygous, 13.3% would be A1 heterozygous, and 3.8% would not carry the A1 allele. Among the 117 subjects homozygous for the HLA B8, DR3 haplotype, only 2 were found to have IgAD (1.7% IgAD). All individuals had normal serum levels of IgG and IgM. Also shown in Table II are the results of three previous studies of IgA deficiency in small populations of HLA B8, DR3 homozygous blood donors. In these cases, the rate of IgA deficiency is much higher than in the larger group we report here.

In order to obtain a measurement of relative risk using our data, we utilized control data from a previously published population-based screening for IgA deficiency in 6,955 blood donors in Sweden, of which 10 were found to be IgA deficient. Importantly, nine of these IgA-deficient blood donors were available for HLA typing. Five carried the HLA B8, DR3 haplotype, but none were homozygous. The rate of HLA B8, DR3 homozygosity in the 6,955 blood donors was not measured, but can be assumed to be less than 1%. Therefore, a reasonable estimate of relative risk for IgA deficiency is not greater that 11.89 (2.63–53.67), p= 0.003, as shown in Table II. If the single missing IgA-deficient subject in the population was HLA B8, DR3 homozygous, the RR would be 13.21 (2.89 to 60.47).

Estimating Relative Risk for IgAD from Case–Control Data

In order to compare these results with our own data, we estimated relative risks from odds ratios derived from HLA typed IgAD cases. Our cohort included 395 IgAD individuals in our immunodeficiency unit (286 IgAD individuals from [26] and 109 recently typed individuals with IgAD).

Table II IgAD in Individuals Homozygous for the HLA B8, DR3 Haplotype

Country	Year	Sample size	IgAD (%)	Type of population	Reference
Australia	1985	14	1(7.1)	Blood donors	[19]
USA	1993	30	4 (13.3)	Blood donors	[20]
USA	1992	10	2 (20)	Blood donors	[21]
		54	7 (13)		Total
Sweden	2008	78	2	Bone marrow donors	This study
		30	0	Family members under investigation for transplantation	
		9	0	Population-based control samples	
		117	2 (1.7)		Total

Of these, 27 are homozygous for the HLA B8, DR3, DQ2 haplotype and 148 are heterozygous for this haplotype.

Additional IgAD individuals were found through routine measurement of IgA serum levels in blood donors throughout various blood centers in Sweden. Of the 28,413 samples measured, 47 were found to be IgAD, of which 17 were available for HLA typing. Two of these samples were homozygous for the B8, DR3, DQ2 haplotype and seven were heterozygous for the haplotype. This material is a subset which represents the samples able to be obtained in a larger material (n=60,477) that has been collected over many years in various blood centers throughout Sweden. It conforms to IgAD prevalence and HLA B8, DR3, DQ2 frequency obtained by serological methods in the entire material (data not shown).

As discussed above, a population-based screening for IgA-deficient blood donors was also previously conducted in Värmland, Sweden to assess the IgA levels in the population [27]. A total of 6,955 blood donors were screened for IgA levels, of which 10 were found to be IgA deficient. These data were pooled into one group of 421 IgAD individuals. Of these, 29 are homozygous for the HLA B8, DR3, DQ2 haplotype and 160 are heterozygous for this haplotype. This indicates a much higher frequency of the haplotype among IgAD individuals (25.9%) compared to the background population of Sweden using data from the Swedish volunteer bone marrow registry (8.2%; $p=5.1\times10^{-74}$, OR=3.90). The frequency of homozygotes for the haplotype was 6.9% in the IgAD group compared with 0.7% in the background population ($p=1.4\times10^{-47}$, OR=11.12), while the frequency of heterozygotes for the haplotype was 38.0% in the IgAD group and 15.3% in the background population ($p=5.3\times10^{-37}$, OR=3.40). Therefore, these estimates of relative risks using cases control calculation of odds ratios are very similar in magnitude to the RR for IgAD suggested by our direct measurement of IgAD risk in HLA B8, DR3 homozygous individuals ascertained solely on the basis of the MHC genotype.

SNP Mapping of the MHC Region of Individuals Homozygous for HLA B8, DR3, DQ2

Results of two SNP maps of the MHC region of individuals homozygous for the HLA B8, DR3, DQ2 haplotype using (a) 1,718 SNPs merged from the IMAGEN project [23] and a genome wide scan (Illumina HumanHap300 beadchip), including 18 Swedish IgAD subjects and 9 population-based controls with normal IgA levels and (b) 3,874 SNPs from a genome wide scan (Illumina Human610-Quad beadchip) on 8 Swedish IgAD subjects and 15 controls from the Swedish volunteer bone marrow registry with normal IgA levels showed no consistent differences in the pattern between the groups (data available upon request). Cases and controls were uniformly homozygous among the measured SNPs with some minor differences throughout, particularly, as expected based on the HLA typing data, upstream of HLA C.

Discussion

Overall, our data provide support for a much more modest effect of homozygosity of the 8.1 haplotype on risk for IgA than suggested previously. Our calculations utilize both direct measurement of IgA prevalence in HLA B8, DR3 homozygous individuals, as well as more standard case–control calculations of odds ratios. The data suggest that the HLA B8, DR3 haplotype acts in a multiplicative fashion; a single copy of the B8, DR3 haplotype carries an estimated RR of approximately 3.4, while two copies of this haplotype carries risk in the 10–12 range. The difference between the results of the present study and earlier reports [19–21] of IgAD in HLA B8, DR3 homozygous individuals might arise from small sample sizes, erroneous tissue typing by serological methods [28, 29], and publication bias. Population heterogeneity is a possible, although unlikely, explanation for the observed differences as frequencies of the 8.1 haplotype and IgAD prevalence are similar across the studied populations. While our study of HLA B8, DR3 homozygotes is still of modest size (n=117), with wide confidence intervals on the RR calculation, the concordance with case–control data is rather strong evidence for the accuracy of the lower risk estimates for homozygosity of the 8.1 haplotype.

Due to a crossover within the class III MHC region, the DR3, DQ2 haplotype in Sardinians is associated with HLA B18 rather than B8 [30]. This observation formed the basis of a previous investigation on whether the IgAD associated gene(s) was localized in the class II or class III region. Thus, Cucca and coworkers [30] measured IgA levels in 43 Sardinian patients with insulin-dependent diabetes mellitus (n=30) or celiac disease (CD; n=13), all homozygous for HLA DR3. Based on the predicted frequency of IgAD in HLA B8, DR3 homozygotes (13%) [19–21], six patients with IgAD were expected but all patients were found to have normal levels of IgA, suggesting that the IgAD predisposing gene is located in the class I or class III region rather than in the class II region. However, the validity of this statement is questioned by our results, showing that only 1.7% of B8, DR3 homozygotes are indeed IgAD, and therefore, only zero to one IgAD patient would have been expected in the cohort of Cucca et al. [30] even if the predisposing gene(s) was located in the class II region.

Homozygosity for the HLA B8, DR3, DQ2 haplotype, or part of this haplotype, also constitutes a risk factor for

development of a variety of autoimmune diseases. Studies on patients with Graves' disease suggest that B8 homozygosity confers an additional risk over heterozygosity of about 3.5-fold to develop the disease [31], while assessment of large numbers of CD patients has shown that 47.4% of the probands are homozygous for DQ2 [32]. Homozygosity for the HLA DR3, DQ2 haplotype has also been described as a risk factor for development of SLE in Scandinavian patients (RR=16.39) [33].

According to data based on our cohort of 421 Swedish IgAD patients, homozygosity and heterozygosity for the B8, DR3, DQ2 haplotype both constitute significant risk factors ($p=1.4\times10^{-47}$ and $p=5.3\times10^{-37}$, respectively) for the development of IgAD, with a limited penetrance. Because of this limited penetrance, we wanted to examine the possibility that other haplotypes may complement the influence of the B8, DR3, DQ2 haplotype on predisposition to IgAD, since this haplotype is found in nearly half of IgAD cases in Sweden. We subsequently examined B8, DR3, DQ2 heterozygotes in both IgAD cases and in the Swedish volunteer bone marrow registry to determine if another HLA allele or haplotype might act in tandem with B8, DR3, DQ2 to cause the disease. DR7 was also found to be associated with IgAD in B8, DR3, DQ2 heterozygotes (21.3%) compared to those in the Swedish volunteer bone marrow registry (8.5%), with a Bonferroni correction for 10 tests yielding a p value of 3.5×10^{-6}; no other HLA alleles were found to be significantly associated with the disease.

As part of this study, we also addressed the hypothesis that a rare, more highly penetrant variant of the 8.1 haplotype might explain the data. Assuming that the Swedish volunteer bone marrow registry represents a cross section of the Swedish population, the frequency of a putative disease predisposing rare variant of the B8, DR3, DQ2 haplotype can be estimated. As mentioned previously, the Swedish bone marrow registry ($n=23{,}609$) contains 136 homozygotes and 3,608 heterozygotes for B8, DR3, DQ2, with an expected 39 IgAD based on the disease prevalence in Sweden (1/600). Since our IgAD patient data indicate that 6.9% are homozygous and 38.0% are heterozygous for the haplotype, we can assume that three of the 39 IgAD in the cohort would be homozygous and 15 heterozygous for the B8, DR3, DQ2 haplotype. The frequency of a rare predisposing haplotype would then be three of 272 in homozygotes and 15 of 3,608 in heterozygotes. Incidentally, the estimate of three IgAD in 136 homozygotes (2.2%) in the Swedish volunteer bone marrow registry using IgAD prevalence and patient haplotypes is similar to the measured frequency of IgAD among known homozygotes (1.7%, two of 117), providing further evidence that the risk of homozygosity for the HLA B8, DR3 haplotype has been overrated. Assuming the existence of a rare, highly penetrant variant of the HLA B8, DR3, DQ2 haplotype, we calculate that an overall frequency of this disease haplotype would be 18 of 3,880 copies (0.46%). If there is such a rare variant in the population, SNP mapping may thus be a useful method to determine if markers of the variant can be discovered and distinguish it in cases versus controls.

Genotyping of SNPs in the MHC region (HLA A to HLA DP) of individuals homozygous for the HLA B8, DR3, DQ2 haplotype (our tested groups) did not, however, show consistent differences between IgAD patients and normal controls (downstream of HLA B). It should be noted though that in the two SNP maps employed, only 1,718 and 3,874 nucleotides of the approximately 3,400,000 present in this region were analyzed. Furthermore, the density of genotyping in the MHC region is limited to known SNPs, while the variation(s) between IgAD patients and controls may lie between these intervals. Hence, a denser SNPs map of the MHC region is required to clarify the influence of potential variants on disease development. Ultimately, full sequencing may be necessary to determine the genetic variant in this haplotype contributing to disease. However, the underlying factor(s) may be located elsewhere in the genome, perhaps being a variant of a given transcription factor, and therefore not able to position using sequencing of the MHC.

Acknowledgments The study was supported by the Swedish Research Council and grant (U19AI067152) from the US National Institute of Allergy and Infectious Diseases. Javad Mohammadi is supported by an educational grant from the Iranian government. We wish to thank Dr. Leonid Padyukov for careful review of the manuscript. We would also like to thank Drs. Leonid Padyukov and Lars Klareskog at the Rheumatology Unit, Department of Medicine at the Karolinska University hospital Solna, Sweden, for supplying some of the control samples used in this study.

References

1. Hammarstrom L, Smith CI. Genetic approach to common variable immunodeficiency and IgA deficiency. In: Ochs H, Smith CI, Puck J, editors. Primary immunodeficiency diseases a molecular and genetic approach. Oxford: Oxford University Press; 2007. p. 313–25.
2. Pan-Hammarstrom Q, Hammarstrom L. Antibody deficiency diseases. Eur J Immunol. 2008;38(2):327–33.
3. Burrows PD, Cooper MD. IgA deficiency. Adv Immunol. 1997;65:245–76.
4. Kanoh T, Mizumoto T, Yasuda N, Koya M, Ohno Y, Uchino H, et al. Selective IgA deficiency in Japanese blood donors: frequency and statistical analysis. Vox Sang. 1986;50(2):81–6.
5. Oen K, Petty RE, Schroeder ML. Immunoglobulin a deficiency: genetic studies. Tissue Antigens. 1982;19(3):174–82.
6. Vorechovsky I, Zetterquist H, Paganelli R, Koskinen S, Webster AD, Bjorkander J, et al. Family and linkage study of selective IgA deficiency and common variable immunodeficiency. Clin Immunol Immunopathol. 1995;77(2):185–92.
7. Vorechovsky I, Webster AD, Plebani A, Hammarstrom L. Genetic linkage of IgA deficiency to the major histocompatibility

complex: evidence for allele segregation distortion, parent-of-origin penetrance differences, and the role of anti-IgA antibodies in disease predisposition. Am J Hum Genet. 1999;64(4):1096–109.
8. Cunningham-Rundles C, Fotino M, Rosina O, Peter JB. Selective IgA deficiency, IgG subclass deficiency, and the major histocompatibility complex. Clin Immunol Immunopathol. 1991;61(2 Pt 2): S61–9.
9. Olerup O, Smith CI, Hammarstrom L. Different amino acids at position 57 of the HLA-DQ beta chain associated with susceptibility and resistance to IgA deficiency. Nature. 1990;347(6290):289–90.
10. MacHulla HK, Schonermarck U, Schaaf A, Muller LP, Kloss C, Kruger J, et al. HLA-A, B, Cw and DRB1, DRB3/4/5, DQB1, DPB1 frequencies in German immunoglobulin A-deficient individuals. Scand J Immunol. 2000;52(2):207–11.
11. Ashman RF, Schaffer FM, Kemp JD, Yokoyama WM, Zhu ZB, Cooper MD, et al. Genetic and immunologic analysis of a family containing five patients with common-variable immune deficiency or selective IgA deficiency. J Clin Immunol. 1992;12(6):406–14.
12. Gual L, Martinez A, Fernandez-Arquero M, Garcia-Rodriguez MC, Ferreira A, Fontan G, et al. Major histocompatibility complex haplotypes in Spanish immunoglobulin A deficiency patients: a comparative fine mapping microsatellite study. Tissue Antigens. 2004;64(6):671–7.
13. Schroeder HW Jr, Schroeder HW 3rd, Sheikh SM. The complex genetics of common variable immunodeficiency. J Investig Med. 2004;52(2):90–103.
14. de la Concha EG, Fernandez-Arquero M, Gual L, Vigil P, Martinez A, Urcelay E, et al. MHC susceptibility genes to IgA deficiency are located in different regions on different HLA haplotypes. J Immunol. 2002;169(8):4637–43.
15. Ammann AJ, Hong R. Selective IgA deficiency: presentation of 30 cases and a review of the literature. Medicine (Baltimore). 1971;50(3):223–36.
16. Badcock LJ, Clarke S, Jones PW, Dawes PT, Mattey DL. Abnormal IgA levels in patients with rheumatoid arthritis. Ann Rheum Dis. 2003;62(1):83–4.
17. Rankin EC, Isenberg DA. IgA deficiency and SLE: prevalence in a clinic population and a review of the literature. Lupus. 1997;6 (4):390–4.
18. Smith WI Jr, Rabin BS, Huellmantel A, Van Thiel DH, Drash A. Immunopathology of juvenile-onset diabetes mellitus. I. IgA deficiency and juvenile diabetes. Diabetes. 1978;27(11):1092–7.
19. Wilton AN, Cobain TJ, Dawkins RL. Family studies of IgA deficiency. Immunogenetics. 1985;21(4):333–42.
20. Kruskall M, Marcus-Bagley D, Awdeh Z, Eisenbarth G, Brink S, Katz A, et al. Many individuals with the MHC conserved extended [HLA -B8, SCO1, DR3] haplotype have immunoglobulin deficiency. Clin Res. 1993;41:277A.
21. Volanakis JE, Zhu ZB, Schaffer FM, Macon KJ, Palermos J, Barger BO, et al. Major histocompatibility complex class III genes and susceptibility to immunoglobulin a deficiency and common variable immunodeficiency. J Clin Invest. 1992;89(6):1914–22.
22. Olerup O, Aldener A, Fogdell A. HLA-DQB1 and -DQA1 typing by PCR amplification with sequence-specific primers (PCR-SSP) in 2 hours. Tissue Antigens. 1993;41(3):119–34.
23. de Bakker PI, McVean G, Sabeti PC, Miretti MM, Green T, Marchini J, et al. A high-resolution HLA and SNP haplotype map for disease association studies in the extended human MHC. Nat Genet. 2006;38(10):1166–72.
24. Avoustin PA, Tkaczuk J, Coppin HL, Cambon-Thomsen A, de Preval C. Extended HLA-DQw2 haplotypes: molecular analysis. Eur J Immunogenet. 1991;18(4):247–57.
25. Awdeh ZL, Raum D, Yunis EJ, Alper CA. Extended HLA/complement allele haplotypes: evidence for T/t-like complex in man. Proc Natl Acad Sci U S A. 1983;80(1):259–63.
26. Mohammadi J, Pourpak Z, Jarefors S, Saghafi S, Zendehdel K, Pourfathollah AA, et al. Human leukocyte antigens (HLA) associated with selective IgA deficiency in Iran and Sweden. Iran J Allergy Asthma Immunol. 2008;7(4):209–14.
27. Bachmann R. Studies on the serum gamma-A-globulin level. 3. The frequency of A-gamma-A-globulinemia. Scand J Clin Lab Invest. 1965;17(4):316–20.
28. Olerup O. Retrospective analysis of HLA-DR typing by serology, TaqI RFLP analysis, and PCR amplification with sequence-specific primers. Transplant Proc. 1994;26(3):1750–1.
29. Schaffer M, Olerup O. HLA-AB typing by polymerase-chain reaction with sequence-specific primers: more accurate, less errors, and increased resolution compared to serological typing. Tissue Antigens. 2001;58(5):299–307.
30. Cucca F, Zhu ZB, Khanna A, Cossu F, Congia M, Badiali M, et al. Evaluation of IgA deficiency in Sardinians indicates a susceptibility gene is encoded within the HLA class III region. Clin Exp Immunol. 1998;111(1):76–80.
31. Farid NR, Barnard JM, Marshall WH. The association of HLA with autoimmune thyroid disease in Newfoundland. The influence of HLA homozygosity in Graves' disease. Tissue Antigens. 1976;8(3):181–9.
32. Zubillaga P, Vidales MC, Zubillaga I, Ormaechea V, Garcia-Urkia N, Vitoria JC. HLA-DQA1 and HLA-DQB1 genetic markers and clinical presentation in celiac disease. J Pediatr Gastroenterol Nutr. 2002;34(5):548–54.
33. Skarsvag S, Hansen KE, Holst A, Moen T. Distribution of HLA class II alleles among Scandinavian patients with systemic lupus erythematosus (SLE): an increased risk of SLE among non [DRB1*03, DQA1*0501, DQB1*0201] class II homozygotes? Tissue Antigens. 1992;40(3):128–33.