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Human Leukocyte Antigens (HLA) Associated with Selective IgA Deficiency in Iran and Sweden

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ABSTRACT

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. There are strong indications for involvement of genetic factors in development of the disease and the frequency of several extended major histocompatibility complex haplotypes (including HLA-A1, B8, DR3, DQ2) have previously been shown to be increased among Caucasian patients with IgAD.

PCR was used to type HLA B, DR, and DQ alleles in 29 Iranian individuals with IgAD and 299 Swedish individuals with IgAD.

The results indicate a strong association with the HLA B14, DR1 alleles in Iranian subjects and HLA B8, B12, B13, B14, B40, DR1, DR3, DR7, DQ2 and DQ5 alleles in Swedish subjects.

Differences in HLA association of IgAD in Iran and Sweden confirm the notion of a genetic background of the disease and that multiple, potentially different genes within the MHC region might be involved in the pathogenesis of IgAD in different ethnic groups.

Key words: Genetic background; HLA antigens; IgA deficiency

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INTRODUCTION

IgA deficiency (IgAD) is the most common primary immunodeficiency in Caucasians with an estimated prevalence of 1/600 (for review see [1]). In contrast, it is only found in 1/18 500 in Japanese,[2] suggesting an ethnic influence on the defect. Many individuals with

IgAD have no apparent disease, whereas some suffer from recurrent infections at mucosal sites, allergies, and autoimmune manifestations.[3,4] A strong familial clustering of the disorder,[5,6] a high relative risk for siblings[7] and an association with selected HLA alleles, suggest involvement of genetic factors in the disease. Autosomal recessive or autosomal dominant inheritance has been shown in some families[5,6] and the defect is presumed to result from impaired switching, or a maturational failure, of IgA-producing lymphocytes.

Numerous studies have examined the relationship between IgAD and the MHC region and an association with the HLA-A1, B8, DR3, DQ2 and B14, DR1 haplotypes has previously been observed. [5,8-16] However, other putative predisposing HLA alleles, including A2, A19, A28, B5, B13, B17 and B40 have also been identified (for review see [1]). Furthermore, a number of negative associations, including B7, DR2, DR5, DR8, DR15, DQB1*0301, DQB1*0602 have previously been reported.[3,13,17-19]

The aim of this study was to evaluate the HLA alleles associated with IgAD in Iran in comparison with another Caucasian (Swedish) population.

PATIENTS AND METHODS

Serum Immunoglobulin Levels

Serum levels of IgG, IgA and IgM were measured by nephelometry in an accredited laboratory. A sample was considered IgAD if the concentration of IgA was below 0.07 g/l.

IgAD Patients

Twenty Iranian IgAD blood donors, recently identified by screening of 13020 individuals[20] and nine patients with IgAD who were referred to the Immunology, Asthma and Allergy Research Institute in Tehran were included in the study, as were 180 Iranian ethnically matched blood donor controls (84 typed for HLA B and 180 typed for HLA DR and DQ). All patients and controls were unrelated Iranian Caucasians.

For comparison, 299 Swedish IgAD patients, diagnosed at the Immunodeficiency Unit at the Karolinska University Hospital Huddinge in Stockholm, were also included in the study (only 286 subjects were typed for the HLA B) as were tissue typing data on 41021 ethnically matched controls (41021 typed for HLA B, 11678 for HLA DR, and 672 for HLA DQ) from the Swedish volunteer bone marrow donor registry (Tobias registry, www.tobiasregistret.se).

HLA Typing

Samples were genotyped at the HLA B, DR and DQ loci using PCR-SSP.[21]

The kits used in this study included the HLA-B low resolution (L21, M26, J82, N80, N02, R56, X13, X82, Y52), the HLA- DQ-DR SSP Combi Tray (K88, R60, V95, M01, M84) and the HLA DQB1*06 high resolution (L 46) from Olerup SSP AB, Saltsjöbaden, Sweden.

Statistical Analyses

Analysis was carried out using the Stata statistical program and the frequencies of IgA in the deficient individuals and control populations and their HLA alleles were compared using Hardy-Weinberg equilibrium, 2X2 contingency tables, chi-square analysis as appropriate. IgAD was associated with several alleles or haplotypes in the MHC region; hence, the relative predispositional effects (RPEs) method[22] was used to determine several associations.

RESULTS

Association with HLA Antigens in Iranian IgAD Patients

Complete HLA typing results on the Iranian individuals with IgAD are given in Table 1. The frequency of HLA B14, DR1 and DQ5 alleles were increased (Table 2) and 2 out of 29 (6.9 %) were homozygous and 7 (24.1 %) were heterozygous for the HLA B14, DR1, DQ5 haplotype ($p>0.05$ and <0.0001 respectively) as compared to controls. No increase in the frequency of the HLA B8, DR3, DQ2 haplotype was, however, noted ($n=1$, $p>0.05$). No individual homozygous for the HLA B14, DR1 or the HLA B8, DR3, DQ2 haplotypes was found in the Iranian control group, where the frequency of individuals heterozygous for the HLA B14, DR1 haplotype was 1.2% (1 out of 84 subjects) and 6% (5 out of 84 subjects) for the HLA B8, DR3 haplotype. Increased frequencies of the HLA B35 (44.8%) and DR7 (27.6%) alleles were also observed in the IgAD group, although not to a statistically significant degree.

Association with HLA Antigens in Swedish IgAD Patients

A strong association with the HLA B8, B12, B13, B14, B40, DR1, DR3, DR7, DQ2 and DQ5 alleles was noted in the Swedish IgAD cohort (Table 3). An increased

frequency of subjects homozygous and heterozygous for the complete HLA B8, DR3, DQ2; HLA DR7, DQ2 and HLA DR1, DQ5 haplotypes was also found (Table 4).

Table 1. Complete HLA typing results of 29 Iranian patients with IgAD

Patient	B	B	DR	DR	DQ	DQ
1	7	57	4	11	3	3
2	44	51	4	10	3	5
3	35	51	1	13	5	6
4	35	55	4	11	3	3
5	14	14	1	13	3	5
6	35	41	7	13	2	6
7	18	35	4	11	3	3
8	35	55	1	7	2	5
9	14	55	1	1	5	5
10	35	55	4	10	2	5
11	50	55	7	11	2	3
12	35	53	1	1	5	5
13	13	15	7	13	2	6
14	13	81	7	11	2	6
15	14	14	1	1	5	5
16	14	14	1	1	5	5
17	8	35	3	3	2	2
18	14	18	1	11	3	5
19	38	50	4	7	2	3
20	14	51	1	4	3	5
21	49	51	4	4	3	3
22	35	35	1	14	5	5
23	35	35	3	13	2	6
24	14	47	1	1	5	5
25	35	52	1	15	5	6
26	14	35	1	11	3	5
27	39	41	3	10	2	5
28	18	44	3	7	2	2
29	14	50	1	7	2	5

Among the Swedish IgAD subjects, 129 out of 286 (45.1 %) carried the full HLA B8, DR3, DQ2 haplotype, either in a homozygous (*n*=19) or heterozygous (*n*=110) form. No patient positive for HLA B8, DR3 but negative for DQ2 was observed. In total, 199 (66.6%) individuals were positive for the HLA DQ2 allele and 57 out of 286 (19.9%) subjects thus carried HLA DQ2 but not B8 (14 samples were not typed for HLA B), most of whom carried the DR7 allele (n=35). In the B8 negative group, the most frequent class I allele was B44 (n=25, 8.4%) followed by B7 (n=15, 5%) and B40 (n=13, 4.3%). Only 8 (2.7%) of the Swedish IgAD patients expressed HLA B8, but not HLA DQ2, a frequency similar to that of controls (4.3%, p>0.05). Sixty out of 299 Swedish individuals with IgAD carried the HLA DR7, DQ2 haplotype (20.1%) and in these subjects, the second most frequent haplotypes were HLA B8, DR3, DQ2 (n=20), HLA DR13, DQ6 (n=9) and HLA DR1, DQ5 (n=5).

Table 2. Positive HLA associations (allele frequency) in Iranian IgAD patients

HLA	IgAD [a]	Controls [b]	OR (CI)	P value [c]
B14	12 (20.7%)	3 (1.8%)	14.3 (3.6-81.3	2×10^{-5}
DR1	19 (32.8%)	24 (6.7%)	6.8 (3.2-14.3)	3.9×10^{-8}
DQ5	23 (39.7%)	75 (20.8%)	2.5 (1.3-4.6)	0.05

[a] The number of alleles typed for the HLA B, DR and DQ = 58 (29 individuals). [b] The number of alleles included in this study as controls for the HLA B= 168 (84 individuals), DR and DQ = 360 (180 individuals), [c] The Bonferroni method was used for correction of the *p* value.

Table 3. Positive and negative HLA associations (allele frequency) in Swedish IgAD patients

HLA	IgAD [a]	Controls [b]	OR (CI)	P value [c]
B8	160 (28%)	9448 (11.5%)	3 (2.5-3.6)	8.8×10^{-33}
B12	90 (15.7%)	10600 (12.9%)	1.6 (1.3-2)	0.001
B13	16 (2.8%)	1270 (1.5%)	2.9 (1.6-4.8)	0.0009
B14	19 (3.3%)	1590 (1.9%)	2.6 (1.5-4.2)	0.001
B40	64 (11.2%)	8174 (10%)	1.6 (1.2-2.2)	0.02
DR1	76 (12.7%)	2602 (11.1%)	1.9 (1.4-2.4)	6×10^{-5}
DR2	22 (3.7%)	3508 (15%)	0.3 (0.2-0.5)	3×10^{-5}
DR3	183 (30.6%)	2355 (10.1%)	3.9 (3.3-4.7)	1.1×10^{-56}
DR7	81 (13.5%)	1853 (7.9%)	2.5 (1.9-3.2)	2.2×10^{-12}
DQ2	260 (43.5%)	259 (19.3%)	3.2 (2.6-4)	3.9×10^{-27}
DQ5	104 (17.4%)	222 (16.5%)	1.7 (1.3-2.3)	0.004
DQ0602	5 (0.8%)	198 (14.7%)	0.07 (0.03-0.18)	1.5×10^{-11}

[a] The number of alleles typed for the HLA B = 572 (286 individuals), DR and DQ = 598 (299 individuals). [b]The number of alleles included in this study as controls for the HLA B = 82042 (41021 individuals), DR =23356 (11678 individuals) and DQ = 1344 (672 individuals). [c]The Bonferroni method was used for correction of the *p* value.

Table 4. Association of inferred HLA haplotypes (haplotype frequency) among Swedish individuals with IgAD

Haplotype	Homozygous			Heterozygous		
	Patients [a] (%)	Controls [b] (%)	*P* (OR, CI)	Patients (%)	Controls (%)	*P* (OR, CI)
B8, DR3, DQ2	19 (6.6)	283 (1.3)	8.1×10^{-21} (7.4, 4.3-12.1)	110 (19.2)	3581 (8.5)	1.8×10^{-22} (2.8, 2.2-3.4)
DR7, DQ2	7 (2.3)	1 (0.1)	5.6×10^{-7} (32.7, 4-1479)	53 (8.9)	51 (3.8)	2.9×10^{-10} (3.5, 2.3-5.3)
DR1, DQ5	8 (2.7)	7 (1)	0.0003 (5.6, 1.7-18.6)	59 (9.9)	121 (9)	0.046 (1.4, 0.98-2)

[a] The number of IgAD patients typed for the complete HLA B, DR, DQ = 286 individuals (572 haplotypes) and HLA DR, DQ = 299 individuals (598 haplotype). [b] The number of controls for the inferred HLA B8, DR3, DQ2 haplotype = 21108 individuals (42216 haplotypes), HLA DR7, DQ2 and HLA DR1, DQ5 haplotypes = 672 individuals (1344 haplotypes).

Among patients heterozygous for the HLA B8, DR3, DQ2 haplotype, HLA B15, DR4, DQ3 was the second most frequent haplotype (n=6) followed by the HLA B44, DR7, DQ2 haplotype (n=5) and the HLA B40, DR13, DQ6 haplotype (n=5). Seventeen (5.9%) of the Swedish patients with IgAD carried HLA B14 (p=0.001). A negative association between IgAD and the DR2 and the DQB1*0602 alleles was also found in the Swedish cohort (Table 3).

DISCUSSION

In this study, we noted a significant increase in the frequency of the HLA B14, DR1 and DQ5 (a border line association) alleles in Iranian IgAD patients, as has also been reported in previous studies from United States,[9,23] Italy,[24] Spain[25] and Australia[14]. In our study, the odds ratio for carrying the B14 and DR1 alleles were 14.3 and 6.8 respectively and these alleles thus appear to be major risk factors for development of IgAD in Iran. Nine of the IgAD subjects (31%) carried the HLA B14, DR1, DQ5 haplotype, 2 (6.9%) of them in a homozygous form. In the normal population, about 1.2% carry this haplotype in a heterozygous form and thus, individuals homozygous for this haplotype are extremely rare.

The majority of IgAD patients in northern Europe, carry the HLA B8, DR3, DQ2 haplotype[3,16,26] whereas in several countries in southern Europe, the HLA B14, DR1 is the most common haplotype among IgAD patients.[24,25] In countries with a high migration rate, such as Australia and United States, IgAD has been found to be associated with both the HLA B8, DR3, DQ2 and the HLA B14, DR1 haplotypes.[8,11,14]

In the present study, to the best of our knowledge, this study is the largest investigation to date in terms of number of HLA typed IgAD subjects. We confirmed previous reports of a strong association with the HLA B8, B12, B13, B14, B40, DR1, DR3, DR7, DQ2 and DQ5 alleles in Swedish patients with IgAD (Table 3)[3,5,10-13,23] as well as a negative association with the DR2 and the DQB1*0602 alleles (Table 3).[13,27] Based on our data, homozygosity and heterozygosity for the HLA B8, DR3, DQ2; the HLA DR7, DQ2 and the HLA DR1, DQ5 (a border line association in the heterozygous form) haplotypes thus constitute strong risk factors for development of IgAD in Sweden (Table 4).[19,27]

Previous studies have suggested that two separate loci, located in the MCH class II and class III regions on different HLA haplotypes, carry susceptibility genes for the development of IgAD.[18,28.29] Thus, a predisposing locus on the HLA DR1 and DR7 positive 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.[18] In our Swedish IgAD patients with complete HLA typing results, 66.1% (189 out of 286) were HLA $DQ2^+$ (HLA $DR7^+$, $DQ2^+$ or HLA $DR3^+$, $DQ2^+$). Only 83.2% (129 out of 155) of the patients with HLA DR3, DQ2 haplotype carried the complete HLA B8, DR3, DQ2 haplotype. Due to the strong LD in the MHC region, the location of the locus associated with IgAD is still controversial [30]. However, our data indicate a dominant influence of the HLA class II region, in particular the DQ2 locus, for development of IgAD in Swedish subjects,[19] where non-aspartic acid at position 57 of the HLA DQβ chain has previously been suggested to be associated with susceptibility to the defect.[19]

It is possible that genes in LD with the HLA B14, DR1 alleles may lead to IgAD by another mechanism than that associated with genes within the HLA B8, DR3, DQ2 haplotype. The mismatch repair proteins MSH5 and MSH4 are critical in safeguarding genetic

stability and are involved in the resolution of Holliday junctions during meiosis.[31] The gene encoding *Msh5* is located within the MHC class III region and Sekine *et al* previously found that hypomorphic mutations in *Msh5* are more often seen in patients with IgAD and common variable immunodeficiency (CVID) than in controls.[32] Two missense mutations, L85F and P786S, were shown to be associated with the ancestral HLA B14, DR1 haplotype. Ig switch region joints from patients carrying this haplotype showed an increase usage of microhomology, suggesting an influence of *Msh5* in facilitating class switch recombination between Sμ and Sα.[32] These findings support the notion of an involvement of a gene(s) located in the MHC class III regions in the pathogenesis of IgAD in a subgroup of patients, i.e. those carrying the HLA B14, DR1, DQ5 haplotype. However, normal IgA levels in controls, heterozygous for the MSH5 missense mutations L85F/P786S, indicates an incomplete penetrance.

Mice with a targeted disruption of *Msh5* are sterile due to an inability to resolve meiotic chromosomal crossovers.[33,34] However, our two Iranian IgAD patients who were homozygous for the HLA B14, DR1 haplotype are both fertile in spite of carrying the L85F/P786S MSH5 mutations in a homozygous form (Ferreira *et al*, unpublished data), suggesting species differences with regard to the role of MSH5 in reproduction.

Differences in HLA association of IgAD in Iran and Sweden confirm the notion of a genetic background of the disease and that multiple, potentially different genes within the MHC region might be involved in the pathogenesis of IgAD in different ethnic groups.

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