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Original Articles

Genetic Association in Familial Common Variable Immunodeficiency (CVID) and IgA Deficiency (IgAD)

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Background/objectives Common variable immunodeficiency (CVID) is a heterogeneous syndrome described by defective antibody production and occurrence of multiple clinical manifestations including autoimmune, lymphoproliferative, and granulomatous diseases. Genes within the major histocompatibility complex (MHC) region have previously been reported to be involved in the pathogenesis of the disease.

Methods To elucidate the human leukocyte antigen (HLA) association, PCR was performed to clarify type HLA B, DR, and DQ alleles in a large sample of Iranian and Swedish CVID patients.

Results No HLA association was observed between Iranian patients with "sporadic" CVID (n=50) and controls. A slight HLA association (B8, DR3, DQ2) was found in Swedish CVID patients (n=95). However, the latter was entirely due to an association in the familial form of the disease. Using 13 informative multiplex families with patients affected by CVID and IgA deficiency (IgAD), shared haplotypes such as HLA-B8-DR3-DQ2; HLA-DR1-DQ5; HLA- DR4- DQ3, and HLA-DR7-DQ2 were observed.

Conclusions Based on our results, we hypothesize that only the familial form of CVID/IgAD may have a common HLA-associated genetic background, whereas "sporadic" cases show no HLA association.

Keywords Common variable immunodeficiency; IgA deficiency HLA; sporadic

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Introduction

Common variable immunodeficiency (CVID) is the most common symptomatic primary immunodeficiency syndrome. It is identified by decreased IgA, IgG levels and, in some patients, reduced IgM levels. These patients have various clinical manifestations, including frequent respiratory and gastrointestinal tract infections, autoimmune and allergic diseases (for review, see [1]).

Selective IgA deficiency (IgAD) is the most common primary immunodeficiency disorder in Caucasians. It is characterized by a reduced serum IgA level (<0.07 g/l) and normal serum levels of IgM and IgG. The majority of these individuals do not manifest disease, whereas some suffer from recurrent infections at mucosal sites, allergies, and autoimmune manifestations (2).

CVID shares many clinical features with IgAD (3), and progression from IgAD to CVID has been reported in several cases (reviewed in [4]). Recessive and dominant modes of inheritance have both been suggested, and IgAD and CVID have occasionally been observed in different members of the same family, suggesting that the same genetic defect may underlie both diseases. In support of this notion, a similar genetic (HLA) predisposition has been found in both CVID and IgAD (5, 6). However, the causal gene defects leading to IgAD and CVID remain unknown. It is likely that the disorders are due to variances in etiologies, and to identify the susceptibility gene(s) for development of the disease, homogenous groups of patients must be investigated.

The aim of this study was to investigate whether a subgroup of CVID patients could be identified using HLA as a selection marker.

Materials and methods

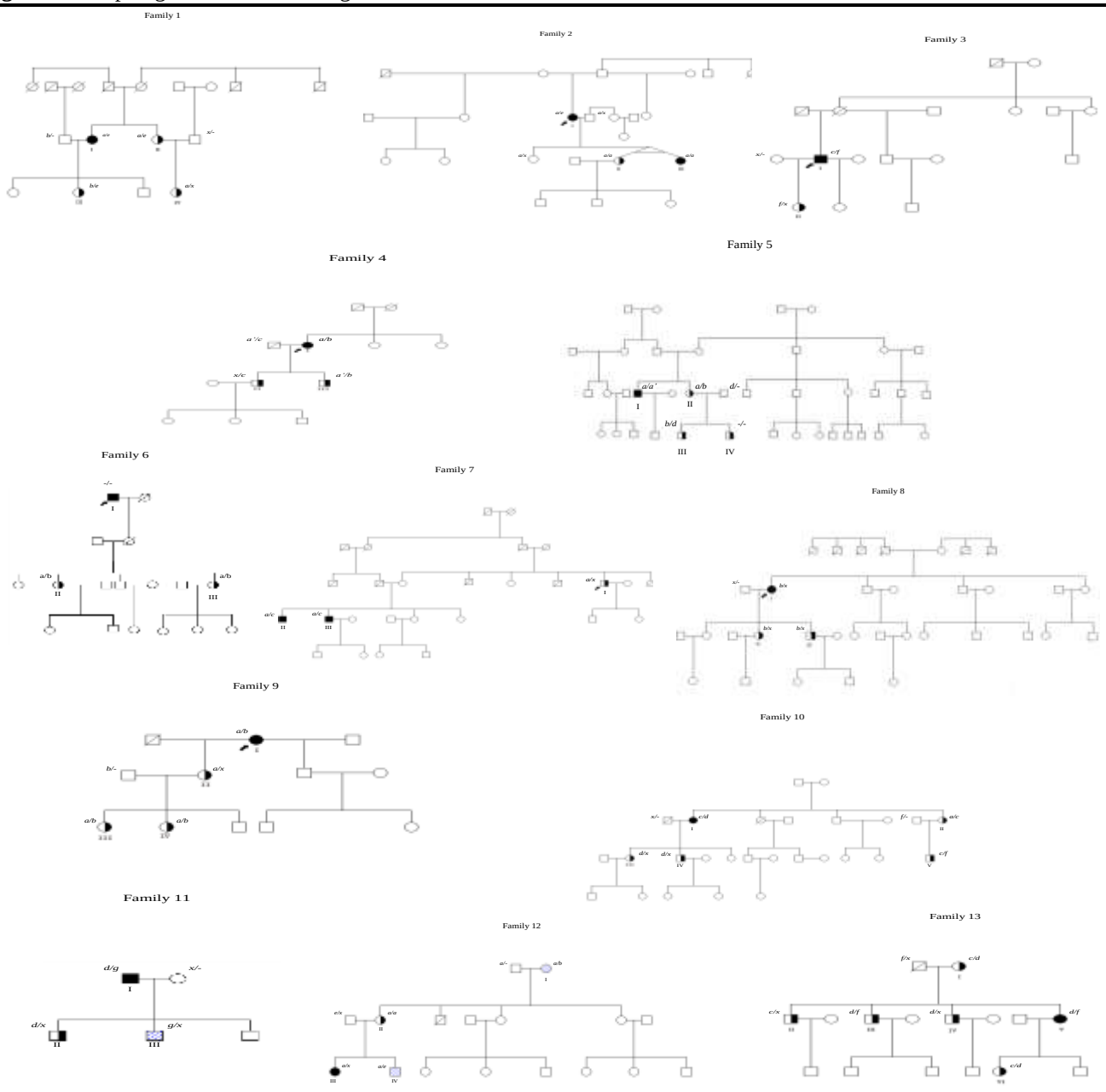
CVID patients

Three groups of Caucasian CVID patients were studied: Iranian, Swedish, and German. Fifty Iranian CVID patients with no family history of immunodeficiency (up to now sporadic) and who were referred to the Immunology, Asthma, and Allergy Research Institute in Tehran, were included in the study as were Iranian, ethnically matched controls (84 typed for HLA B and 180 typed for HLA DR and DQ). All patients and controls were unrelated Iranian Caucasians. The pedigrees of CVID and IgAD families are demonstrated in **Figure 1**.

For comparison, 95 CVID patients, diagnosed at the Immunodeficiency Unit at the Karolinska University Hospital Huddinge in Stockholm, were also included in the study as were tissue typing data on 41021 Swedish ethnically matched controls (41,021 typed for HLA B, 11,678 for HLA DR, and 672 for HLA DQ) from the volunteer bone marrow donor registry (Tobias registry, www.tobiasregistret.se). Most cases were sporadic (n=84), but 11 had family members with immunodeficiencies (multiplex families comprising.

13 subjects with CVID and 21 with IgAD). In addition, three German multiplex families with 3 members with CVID, 7 with IgAD, and 3 with dysgammaglobulinemia were included in this study.

Figure 1. The pedigrees of CVID and IgAD families



In family I, affected members including I (CVID), II (IgAD) and IV (IgAD) all share the haplotype *a*. In family 2, two haploidentical siblings-CVID (III) and IgAD (II) have inherited the same haplotype (*a*) in a homozygous form from their parents. Their mother (proband) suffers from CVID (I). The patients' father, however, HLA identical to the affected siblings, was not affected; Arrow = Proband. In family 3, the IgAD daughter inherited the same haplotype (*f*) from her mother with CVID. In family 4, the concurrence of CVID and IgAD in a mother and her sons, respectively is shown. Patients I and III shared haplotype *a'*. IgAD patient II has a different haplotype from his mother. In the latter patient, a recombination event may have happened between the DQ5 and DR regions. In family 5, the IgAD mother gave the haplotype *b* to her IgAD children. However, her haploidentical (*a*) brother with CVID did not have antibody deficient children. In family 6, two haploidentical sisters (II, III) are IgAD. Their grandfather suffered from CVID (I). In family 7, two haploidentical brothers with CVID have an IgAD uncle with the same haplotype (*a*). In family 8, two siblings with IgAD have inherited the same haplotype (*b*) from their mother who suffers from CVID.

In family 9, three generations with CVID and IgAD possessed the same haplotype (*a*). Also, two sisters with IgAD (III, IV) carried haplotype *b*, similar to their grandmother (I).
In family number 10, two IgAD siblings have inherited the same haplotype (*d*) from their mother with CVID. Their IgAD aunt (II) transmitted the same haplotype (*c*) to her son (V) that is identical to her sister (patient I). In family 11, the IgAD patient inherited the haplotype *d* from his father with CVID. His brother, who has IgG subclass deficiency and IgA deficiency, inherited haplotype *g* from his father as well. The shaded box or circle = patients in families who have IgG subclass deficiency with IgA deficiency and no recurrent infections. In family 12, all immunodeficient individuals (I, II, III, IV) in three generations possessed identical haplotype (*a*). Individual number I and her grandson (IV) both have low levels of IgG subclass and IgA. The mother with IgAD is homozygous for the haplotype *a*. In family 13, the grandmother with IgAD (I) distributed identical haplotype (*d*) to her three affected children, two with IgAD (III, IV) and one with CVID (V). Also, the CVID patient transmitted haplotype *d* to her daughter with IgAD (VI). On the other hand the IgAD son (II) inherited the haplotype *c* from his mother with IgAD (I).
• Solid box or circle = Common variable immunodeficiency, Semisolid box or circle = IgA deficiency. Haplotype HLA B8, DR3, DQ2 = a-, Haplotype HLA DR3, DQ2 = a'-, Haplotype HLA DR1, DQ5 = b, Haplotype HLA DR4, DQ3 = c, Haplotype HLA DR7, DQ2 = d, Haplotype HLA DR7, DQ3 = e, Haplotype HLA DR15, DQ6 = f, Haplotype HLA B35, DR14, DQ5 = g, other haplotypes = x, Haplotype same with x in two alleles = x', Not determined haplotypes = -.

IgAD patients

To determine the HLA association between CVID and IgAD, data on 386 Swedish sporadic and 56 Swedish familial IgAD patients and 29 Iranian sporadic patients with IgAD were also analyzed in this study. All Iranian and 299 (49 familial and 250 sporadic) Swedish individuals with IgAD who were included in the present study have been described previously (7).

Serum immunoglobulin levels

Serum levels of IgG, IgA and IgM were measured by nephelometry. The diagnosis of CVID and IgAD was made using ESID criteria (www.esid.org).

HLA typing

Samples were genotyped at the HLA B, DR, and DQ loci using PCR-SSP (8). The kits utilized in the present 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

The analysis was performed by the Stata statistical program, and the frequencies of the HLA alleles and haplotypes were compared using Hardy-Weinberg equilibrium, 2x2 contingency tables, chi-square analysis, and Fisher's exact test and the Bonferroni method. IgAD and CVID were associated with multiple alleles or haplotypes in the MHC region; thus, the relative predisposition effects (RPEs) method (9) was used to determine several associations.

Results

No HLA association was found in Iranian patients with sporadic CVID as compared with controls. The comparison of HLA alleles between Iranian CVID patients and Iranian IgAD patients showed no similarity between their MHC class I and II alleles (all $p<0.05$). A slight, negative association with HLA B15 ($p=0.038$) was found in the Swedish CVID patients (combined sporadic and familial).

In Swedish sporadic CVID patients (data not shown), a positive association with HLA DR9 ($p=0.03$) was observed, and 16 out of 84 (19%) carried the HLA B8, DR3, DQ2 haplotype, one in a homozygous form (**Table 1**). Four (4.2%) Swedish

CVID patients carried the HLA DQ2 allele in a homozygous form; however, this frequency was not significantly different from the controls.

Interestingly, in the Swedish familial CVID patients, a significant increase in the frequency of the HLA B8, DR3, and DQ2 alleles was observed (**Table 2**) as were the complete HLA B8, DR3, DQ2 and the HLA DR7, DQ2 haplotypes in a heterozygous form (**Table 1**).

Analysis of the HLA alleles shared between Swedish CVID (combined familial and sporadic) and IgAD (combined familial and sporadic) patients showed a similarity in HLA DR7 only ($p>0.05$). In Swedish individuals with sporadic IgAD (n=386), a strong association with the HLA B8, B12, B13, B14, DR1, DR3, DR5, DR6, DR7, DR9, DQ2, DQ5, and DQ6 (non-DQ0602) alleles as well as a negative association with the HLA B7, B15, DR2 and DQ0602 alleles was found (Table 3). In this group of patients, an increased frequency of subjects homozygous and heterozygous for the complete HLA B8, DR3, DQ2; HLA DR1, DQ5; HLA DR7, DQ2 and the HLA DR13, DQ6 haplotypes was also noted (**Table 4**). In subjects positive for the DR7, DQ2 haplotype, the most frequent inferred class I allele was B44 (n=16) followed by B13 (n=15).

In individuals with familial IgAD, a strong association with the HLA B8, DR3, DR7, and DQ2 alleles was also seen (**Table 3**). In the latter IgAD group, heterozygosity for the HLA B8, DR3, DQ2 haplotype and homozygosity and heterozygosity (a borderline association) for the HLA DR7, DQ2 haplotype constituted risk factors for the development of IgAD (**Table 4**). In addition, among individuals with familial IgAD positive for the HLA DR7, DQ2 haplotype, the most frequent inferred class I allele was B44 (n=3).

Assessment of the HLA antigens in Swedish familial CVID and familial IgAD (patients with family members with immunodeficiency) showed a sharing of the HLA B8, DR3, DR7, and DQ2 alleles (all $p>0.05$, **Table 5**). Furthermore, a sharing of the B15 ($p>0.05$) and the DR7 alleles ($p>0.05$) in Swedish sporadic CVID and Swedish sporadic IgAD was also found.

Table 1. Associations of the HLA B8, DR3, DQ2 and the HLA DR7, DQ2 haplotypes in Swedish patients with familial and sporadic CVID compared to controls

Haplotype	Form	Familial (*n*=11) [a]	*P* value	Sporadic (*n*=84)	*P* value	Controls [a]
B8, DR3, DQ2	Homozygous	1 (9%)	NS [b]	1 (1.2%)	NS	283 (1.3%)
	Heterozygous	6 (27.3%) [c]	0.002	18 (810.7%)	NS	3581 (8.5%)
DR7, DQ2	Homozygous	0 (0%)	NS	2 (2.4%)	NS	1 (0.5%)
	Heterozygous	3 (13.6%)	0.01	6 (3.6%)	NS	55 (4.1%)

[a] Number of patients and controls (for the HLA B8, DR3, DQ2 =21108 and for the HLA DR7, DQ2=672)
[a] NS=Not significant
[c] The percentage of heterozygous individuals based on number of haplotypes

Table 2. HLA associations (allele frequency) in Swedish familial CVID patients compared to controls

HLA	CVID (*n*=22) [a]	Controls [a, b]	*P* value [c]	OR (CI)
B8	8 (36.4%)	9448 (11.5%)	0.006	4.4 (1.6-11.2)
DR3	9 (40.9%)	2355 (10.1%)	3.3×10^{-5}	6.2 (2.3-15.6)
DQ2	11 (50%)	259 (19.3%)	0.006	4.2 (1.6-10.8)

[a] Allele frequency
[b] HLA B= 82042, DR n=23356, DQ n=1344
[c] The Bonferroni method was used for correction of the *p* value

Table 3. Allele frequency in Swedish individuals with IgAD (familial and sporadic) compared to controls

Allele	Familial	*P* value [b], OR	Sporadic	*P* value, OR	Controls [c]
	Case (n=112) [a]		Case (n=772)		
B7	10	NS	51	0.004, 0.55	12152
B8	34	1.4×10^{-8}, 3.4	199	1.9×10^{-36}, 2.8	9448
B12	16	NS	115	0.0007, 1.6	10600
B13	3	NS	25	3.2×10^{-7}, 3.1	1270
B14	4	NS	32	8.9×10^{-9}, 3.1	1590
B15	11	NS	26	4.1×10^{-5}, 0.38	9285
DR1	11	NS	111	2.4×10^{-9}, 2.1	2602
DR2	5	NS	26	0.004, 0.4	3508
DR3	43	1.8×10^{-21}, 5.6	218	1.5×10^{-57}, 3.5	2355
DR5	7	NS	44	0.03, 1.8	1805
DR6	13	NS	133	0.004, 1.5	3724
DR7	14	0.03, 2.6	108	4.1×10^{-30}, 3.8	1853
DR9	1	NS	13	0.02, 2.7	363
DQ2	57	1.9×10^{-13}, 4.3	312	2.2×10^{-25}, 2.9	259
DQ5	19	NS	143	7.8×10^{-5}, 1.8	222
DQ (non-0602)	7	NS	103	3×10^{-4}, 1.9	180
DQ0602	5	NS	18	1.3×10^{-9}, 0.11	198

[a] Number of familial patients=56; sporadic patients =386

[b] The Bonferroni method was used for correction of the *p* value

[c] Number of controls for the HLA B=82042, DR=23356, and DQ=1344

Table 4. Associations of the HLA B8, DR3, DQ2, the HLA DR7, DQ2, and the HLA DR1, DQ5 haplotypes among Swedish patients with familial and sporadic IgAD

Haplotype	Form	Familial (*n*=56) [a]	*P* value	Sporadic (*n*=386) [a]	*P* value	Controls [b]
B8, DR3, DQ2	Homozygous	2 (3.6%)	NS	24 (6.2%)	1.2×10^{-15}	283 (1.3%)
	Heterozygous	29 (25.9%) [c]	4.5×10^{-11}	158 (20.5%)	1.6×10^{-35}	3581 (8.5%)
DR7, DQ2	Homozygous	2 (3.6%)	0.0001	6 (1.6%)	0.004	1 (0.1%)
	Heterozygous	8 (7.1%)	0.058	76 (9.8%)	6.8×10^{-16}	60 (4.5%)
DR1, DQ5	Homozygous	1 (1.8%)	NS	14 (3.6%)	0.002	7 (1.4%)
	Heterozygous	9 (8%)	NS	81 (10.5%)	0.0002	121 (9%)
DR13, DQ6	Homozygous	0	NS	8 (2.1%)	0.008	3 (0.4%)
	Heterozygous	6 (5.4%)	NS	82 (10.6%)	0.005	124 (9.2%)

[a] Number of patients

[b] Number of controls for the HLA B8, DR3, DQ2 haplotype=21108 and for the HLA DR7, DQ2 and the HLA DR1, DQ5 haplotypes=672

[c] The percentage of heterozygous individuals are based on number of haplotypes

Table 5. Similarities in the HLA B, DR and DQ loci in Swedish familial CVID as compared to Swedish familial IgAD patients [a]

HLA	CVID (*n*=22) [b]	IgAD (*n*=112) [b]	*P* value
B8	8 (36.4%)	34 (30.1%)	>0.05
DR3	9 (40.9%)	43 (38.4%)	>0.05
DR7	3 (13.6%)	14 (12.5%)	>0.05
DQ2	11 (50%)	57 (50.9%)	>0.05

[a] No significant difference in the HLA B8, DR3, DQ2 between the two patient groups was observed.

[b] Allele frequency

Multiplex families

Assessment of the haplotypes in 13 multiplex families (families with both CVID and IgAD, families 1-10 were Swedish and 11-13 were German) with 46 affected individuals showed that 24 out of 46 (52.1%) carried the HLA DR3, DQ2 haplotype (haplotype *a*), 4 of them in a homozygous form. Thirteen out of 46 (28.3%) carried the HLA DR1, DQ5 haplotype (haplotype *b*), 11 out of 46 (23.9%) carried the HLA DR4, DQ3 haplotype (haplotype *c*) and 10 out of 46 (21.7%) carried the HLA DR7, DQ2 haplotype (haplotype *d*) (**Table 6**). Among the 13 multiplex families, three individuals with IgAD and two CVID patients carried the HLA DQB1* 0602 alleles which have been suggested to be protective for the development of IgAD (10).

Table 6. Family data of the multiplex families (CVID patients with IgAD relatives)

			Haplotype 1			Haplotype 2		
Family	**ID**	**Disorder**	**HLA B**	**HLA DR**	**HLA DQ**	**HLA B**	**HLA DR**	**HLADQ**
1	I	CVID	8	3	2	57	7	3
1	II	IgAD	8	3	2	57	7	3
1	III	IgAD	18	1	3	57	7	3
1	IV	IgAD	8	3	2	7	4	3
2	I	CVID	8	3	2	18	4	3
2	II	IgAD	8	3	2	8	3	2
2	III	CVID	8	3	2	8	3	2
3	I	CVID	7	15	6*	55	4	3
3	II	IgAD	7	15	6*	51	13	6
4	I	CVID	8	3	2	7	1	5
4	II	IgAD	7	4	3	7	14	5
4	III	IgAD	40	3	2	35	1	5
5	I	CVID	8	3	2	44	3	2
5	II	IgAD	8	3	2	15	1	5
5	III	IgAD	53	7	2	15	1	5
6	I	CVID	- [a]	-	-	-	-	-
6	II	IgAD	8	3	2	14	1	5
6	III	IgAD	8	3	2	14	1	5
7	I	IgAD	8	3	2	7	12	3
7	II	CVID	8	3	2	47	4	3
7	III	CVID	8	3	2	47	4	3
8	I	CVID	7	13	6	44	1	5
8	II	IgAD	35	14	5	44	1	5
8	III	IgAD	35	14	5	44	1	5
9	I	CVID	8	3	2	27	1	5
9	II	IgAD	8	3	2	27	1	2
9	III	IgAD	8	3	2	27	1	5
9	IV	IgAD	8	3	2	27	1	5
10	I	CVID	27	4	3	44	7	2
10	II	IgAD	35	8	4	44	7	2
10	III	IgAD	35	8	4	44	7	2
10	IV	IgAD	8	3	2	47	3	3
10	V	IgAD	47	4	3	7	15	6*
11	I	CVID	13	7	2	35	14	5
11	II	IgAD	13	7	2	51	13	6
11	III	Dys	51	13	6	35	14	5

12	I	Dys	8	3	2	55	1	5
12	II	IgAD	8	3	2	8	3	2
12	III	Dys	8	3	2	57	7	3
12	IV	CVID	8	3	2	51	12	3
13	I	IgAD	35	4	3	18	7	2
13	II	IgAD	35	4	3	44	13	6
13	III	IgAD	7	15	6*	18	7	2
13	IV	CVID	7	15	6*	18	7	2
13	V	IgAD	44	13	6	18	7	2
13	VI	IgAD	37	4	3	18	7	2

[a]- = Not determined

Discussion

No association was found between HLA antigens and sporadic CVID in Iran, as has also been observed in previous studies in other ethnic populations (3, 11-13). Despite the high prevalence (66.2%) of consanguineous marriages among these families, no familial case was seen (14), suggesting that they may represent a subgroup of the disorder. Furthermore, Iranian individuals with IgAD showed an over-representation of the HLA B14, DR1, and DQ5 alleles (7). However, only 4.1% (2 out of 49) of the Iranian CVID patients carried the HLA B14, DR1, DQ5 haplotype, all in a heterozygous form, a frequency similar to that of the controls (1.2%). The data thus suggested that different predisposing genetic factors in the MHC class I and II regions are involved in the development of sporadic IgAD and CVID in Iran.

The weak association between Swedish sporadic CVID and the HLA DR9 supported the notion of involvement of non-MHC region (more than MHC region) in the development of sporadic CVID.

In Swedish patients with familial CVID, a strong association with the HLA B8, DR3, DQ2 alleles was noted (Table 2), suggesting a different genetic predisposition than the sporadic form of the disease, and the heterozygosity for the HLA B8, DR3, DQ2 and the HLA DR7, DQ2 haplotypes constitutes risk factors for the development of CVID in the familial form (Table 1).

Investigators have previously suggested an additive effect of susceptibility loci with individuals homozygous for the MCH class II loci for the development of CVID (3, 12). However, according to our assessment, the frequencies of the CVID subjects (combined familial and sporadic forms) homozygous for MHC class II alleles were similar to those of the controls (data not shown).

In the present study, which used an additional 136 Swedish sporadic IgAD subjects, in addition to the authors' previous findings (7), a strong association with the HLA DR5, DR6, DR9 and DQ6 (DQ non-0602) alleles was noted; however, the frequency of B40 did not reach a significant level (Table 3). In sporadic IgAD, all risk haplotypes in addition to a new risk haplotype - the HLA DR13, DQ6 - were increased in frequency (Table 4). The number of limited HLA markers shared between the sporadic and familial form of IgAD suggested that these two forms of immunodeficiencies may represent genetically different disorders.

Based on previous observations, only a few individuals with CVID share a common underlying genetic defect with IgAD (3, 11). In a study of multiplex families by Volanakis *et al.* (11), 77% (24 out of 31) of patients with CVID and IgAD carried the whole, or part of, the ancestral HLA B8, DR3 and/or HLA DR7, DQ2 haplotypes.

Subsequently, we investigated Swedish familial CVID and familial IgAD, and a similarity in the HLA B8, DR3, DR7 and DQ2 loci between the two immunodeficiency disorders was observed (Table 5). Strikingly, in the familial form of CVID and IgAD, the HLA DQ2 allele was the most frequent allele (50% and 50.9% respectively) (Table 5), suggesting an influence of this locus for the development of IgAD and CVID in familial cases.

In our sporadic CVID and IgAD patient groups, the weak HLA similarities suggest that different genetic susceptibility elements are involved in the pathogenesis of the two immunodeficiencies in the sporadic form.

Another important observation in the present study was that a few HLA haplotypes were frequently noted in multiplex families. Among these patients, at least one copy of the HLA B8, DR3, DQ2 (haplotype *a*); DR1, DQ5 (haplotype *b*); DR4, DQ3 (haplotype *c*); or DR7, DQ2 (haplotype *d*) haplotypes was observed in 93.3% of cases as has been previously reported (11). No differences were found between CVID and IgAD in terms of the distribution of these haplotypes. These findings provide further support to the hypothesis that IgAD and CVID are associated with particular HLA haplotypes in the familial form (11, 12).

No differences were observed in the distribution of the selected haplotypes in families with autosomal dominant or autosomal recessive inheritance.

In the present study, an increased frequency of familial IgAD with autosomal dominant inheritance (22 out of 28, 78.6%) was observed as compared to familial CVID subjects (3 out of 12, 25%) (p=0.002), suggesting a dominant role for the selected haplotypes in the development of familial IgAD with autosomal dominant mode of inheritance as compared to familial CVID.

Conclusion

The current analysis of the alleles within the MHC class I and class II regions in a large sample size comprised of CVID and IgAD subjects provides evidence that the majority of CVID and IgAD patients (sporadic form) possess different predisposing gene(s) in the MHC region, and that a causal relationship exists between CVID and IgAD in multiplex families. Consequently, a genetic heterogeneity model would suggest that CVID is not a single disease, but rather represents several etiologically and phenotypically distinct diseases presenting a similar clinical picture.

Conflict of interest

The authors declare no conflict of interest.

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