Original Article

HLA Profile in Iraqi Rheumatic Valvulitis Patients

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Summary:

***Background**: Human leukocyte antigen (HLA) is the most polymorphic genetic system in man. The genes of this region influence susceptibility to certain disease.*
***Objectives**: This study was established to shed light on the possible association of HLA class I and II antigens with RV patients.*
***Patients and Methods**: Lymphocytotoxicity assay for HLA for class I and II typing had been done for (100) Iraqi patients suffering from rheumatic valvulitis (RV), the control groups consisting of (75 healthy individuals and 35 non rheumatic heart disease (NRHD) patients).*
***Results**: The results showed a significant association of A33-Ags with these patients as compared with healthy and cardiac controls (P=0.005), (P=0.033) respectively. Another interesting finding was the low frequency of A1 in RV patients when compared with healthy control (p=0.002), suggesting that A1 allele may confer protective effect against this disease. In addition significant association between blood group B and RV was evident (p=0.04). An interesting observation was a strong association of blood group B and A33 among those patients (P<0.001).*
***Conclusion**: The present results are consistent with hypothesis that susceptibility to RV is genetically linked and in turn may be associated mainly with A33 in Iraqi patients.*
***Key words:** HLA, rheumatic valvulitis*

Introduction:

HLA system is used to study the immunogenic basis of some diseases with known or suspected hereditary factors and / or with a possible immunological basis (1). Extensive information links certain HLA alleles and susceptibility to certain diseases. Among which are some autoimmune disease, viral disease, disorder of complement system and several different allergic conditions (2).

Rheumatic fever is a delayed sequal to group A streptococcal pharyngitis, of an autoimmune origin. The medical importance of rheumatic fever is serious cardiac involvement with valvulitis (rheumatic valvulitis) which may lead to death or valve replacement (3). Acquired mitral valve stenosis (MS) is virtually synonymous with RHD, it is a life long and sometimes progressive disease (4). Approximately 35% of patients with rheumatic fever will develop RHD later in life (5). The severity of RHD is generally proportional to the severity of acute carditis.

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An increased or decreased incidence of certain HLA alloantigens has been reported with RHD by some investigators (6,7). The aim of the work is to study the association of HLA and RV in Iraqi patients.

Subjects and Methods:

Patients:

Patients with RV (one hundred cases) had been studied over ten months period from march 2002 till December of the same year, their age was range from 18-64 years. Females constitute sixty six while the number of males were thirty four.Diagnosis was made by specialized cardiologist in the Ibn Al-Betar heart hospital.

Controls:

1 - Healthy controls: Blood samples had been drawn from 75 healthy individuals who are age, gender and ethnic matched with patients.
2 - Patients with heart diseases other than rheumatic were choosen as a second control(35 patients). It included cases with congenital heart abnormality and degenerative cardiac diseases.

Methods:

HLA typing:

10 ml of venous blood had been drawn from patients and controls, typing for HLA class I and II (HLA-A, B,C, DR and DQ antigens) was carried out in the teaching laboratories of Medical City. The microlymphocytotoxicity test which had been established by (Terasaki and McClelland, 1964) (8)

and modified by (Dick and Kissmeyer, 1979)(1) and (Bender, 1984)(9) was followed.

Statistical Analysis:

Univariate analysis has been applied for the data depending on logistic regression and the results were reported as odds ratio (OR), which represented the increased or decreased risk for RV. An estimate was considered statistically significant if P value was less than an α level of significance of 0.05.

Results:

The frequency distribution of various class I and II of HLA-Ags for study groups was presented in tables (1,2). A significant association was found between RV patients and A33, the frequency distribution was 27% in patients versus 9.3% in healthy control, OR = 3.6, p= 0.005, EF= 0.195 (Table 1). In the second control (non rhaumatic heart disease) frequency distribution was equal to 8.6%, OR= 3.9, p= 0.033, EF= 0.202 (Table 2).

Appreciable decrease in the antigen frequency of A1 was noticed in RV patients 6% as compared with control (healthy individuals) 22.7%, inverse OR= 4.6, p=0.002, PF= 0.177 (Table 1). While the frequency was 14.3% in the 2nd control (NRHD) which is not significant when compared with the RV patients, inverse OR= 2.6, p= NS, PF= 0.088 (Table 2). Results were tabulated in relation to studies from other countries. Table 3 shows literature data about the association of HLA phenotype with RF & RHD in different ethnic groups. The results of the ABO blood groups in RV patients were shown in table (4). There was significant increase in the blood group B frequency (P= 0.04) of the RV patients as compared with controls. The blood group B antigens showed a strong association among RV patients with A33-Ag (p < 0.001) table (5).

Table 1: Antigens frequency of the HLA- class I & II of the RV patients and the healthy controls.

	Healthy controls No.(%)	*RV cases No.(%)*	*OR*	*Inverse OR*	*P*	*EF*	*PF*
HLA -A							
1	***17(22.7)***	***6(6.0)***	***0.2***	***4.6***	***0.002***	**	***0.177***
2	***28(37.3)***	***35(35.0)***	***0.9***	***1.1***	***NS***	**	***0.036***
3	***14(18.7)***	***18(18.0)***	***1.0***	***1.0***	***NS***	**	***0.008***
9	***3(4.0)***	***6(6.0)***	***1.5***	**	***NS***	***0.021***	**
10	***1(1.3)***	***3(3.0)***	***2.3***	**	***NS***	***0.017***	**
11	***9(12.0)***	***18(18.0)***	***1.6***	**	***NS***	***0.068***	**
23	***3(4.0)***	***3(3.0)***	***0.7***	***1.3***	***NS***	**	***0.010***
24	***13(17.3)***	***12(12.0)***	***0.7***	***1.5***	***NS***	**	***0.06***
25	***1(1.3)***	***3(3.0)***	***2.3***	**	***NS***	***0.017***	**
26	***7(9.3)***	***15(15.0)***	***1.7***	**	***NS***	***0.063***	**
28	***9(12.0)***	***18(18.0)***	***1.6***	**	***NS***	***0.068***	**
29	***3(4.0)***	***1(1.0)***	***0.2***	***4.1***	***NS***	**	***0.030***
30	***12(16.0)***	***15(15.0)***	***0.9***	***1.1***	***NS***	**	***0.012***
31	***2(2.7)***	***0(0.0)***	***0.1***	***6.8***	***NS***	**	**
32	***2(2.7)***	***0(0.0)***	***0.1***	***6.8***	***NS***	**	**
33	***7(9.3)***	***27(27.0)***	***3.6***	**	***0.005***	***0.195***	**
34	***1(1.3)***	***3(3.0)***	***2.3***	**	***NS***	***0.017***	**
36	***1(1.3)***	***0(0.0)***	***0.2***	***4.0***	***NS***	**	**
Blank	***17(22.7)***	***17(17.0)***					**
total	***150(100)***	***200(100)***					
HLA-B							
5	***3(4.0)***	***6(6.0)***	***1.5***	**	***NS***	***0.021***	**
7	***8(10.7)***	***6(6.0)***	***0.5***	***1.9***	***NS***	**	***0.050***
8	***8(10.7)***	***18(18.0)***	***1.8***	**	***NS***	***0.082***	**
12	***0(0.0)***	***3(3.0)***	***5.4***	**	***NS***	***0.024***	**
13	***5(6.7)***	***9(9.0)***	***1.4***	**	***NS***	***0.025***	**
14	***4(5.3)***	***9(9.0)***	***1.8***	**	***NS***	***0.039***	**
15	***1(1.3)***	***0(0.0)***	***0.2***	***4.0***	***NS***	**	**
17	***5(6.7)***	***6(6.0)***	***0.9***	***1.1***	***NS***	**	***0.007***
18	***3(4)***	***3(3)***	***0.7***	***1.3***	***NS***	**	**
21	***1(1.3)***	***0(0.0)***	***0.2***	***4.0***	***NS***	**	**
22	***0(0.0)***	***4(4.0)***	***7.0***	**	***NS***	***0.034***	**
27	***3(4.0)***	***3(3.0)***	***0.7***	***1.3***	***NS***	**	***0.010***
35	***13(17.3)***	***12(12.0)***	***0.7***	***1.5***	***NS***	**	***0.061***
37	***3(4.0)***	***8(8.0)***	***2.1***	**	***NS***	***0.042***	**
38	***5(6.7)***	***6(6.0)***	***0.9***	***1.1***	***NS***	**	***0.007***

39	*1(1.3)*	*3(3.0)*	*2.3*	**	*NS*	*0.017*	**
40	*2(2.7)*	*0(0.0)*	*0.1*	*6.8*	*NS*	**	**
41	*9(12.0)*	*6(6.0)*	*0.5*	*2.1*	*NS*	**	*0.064*
44	*6(8.0)*	*3(3.0)*	*0.4*	*2.3*	*NS*	**	*0.038*
45	*1(1.3)*	*3(3.0)*	*2.3*	**	*NS*	*0.017*	**
47	*1(1.3)*	*0(0.0)*	*0.2*	*4.0*	*NS*	**	**
49	*6(8.0)*	*9(9.0)*	*1.1*	**	*NS*	*0.011*	**
50	*9(12.0)*	*15(15.0)*	*1.3*	**	*NS*	*0.034*	**
51	*14(18.7)*	*9(9.0)*	*0.4*	*2.3*	*NS*	**	*0.106*
52	*3(4.0)*	*3(3)*	*0.7*	*1.3*	*NS*	**	**
53	*3(4.0)*	*3(3.0)*	*0.7*	*1.3*	*NS*	**	*0.010*
54	*0(0.0)*	*3(3.0)*	*5.4*	**	*NS*	*0.024*	**
55	*1(1.3)*	*0(0.0)*	*0.2*	*4.0*	*NS*	**	**
56	*1(1.3)*	*0(0.0)*	*0.2*	*4.0*	*NS*	**	**
57	*1(1.3)*	*6(6.0)*	*4.7*	**	*NS*	*0.047*	**
60	*0(0.0)*	*3(3.0)*	*5.4*	**	*NS*	*0.024*	**
62	*1(1.3)*	*3(3.0)*	*2.3*	**	*NS*	*0.017*	**
63	*1(1.3)*	*0(0.0)*	*0.2*	*4.0*	*NS*	**	**
70	*1(1.3)*	*0(0.0)*	*0.2*	*4.0*	*NS*	**	**
73	*0(0.0)*	*3(3.0)*	*5.4*	**	*NS*	*0.024*	**
Blank	*27(36)*	*35(35)*					
Total	*150(100)*	*200(100)*					
HLA-C							
1	*2(2.7)*	*3(3.0)*	*1.1*	**	*NS*	*0.003*	**
2	*5(6.7)*	*12(12.0)*	*1.9*	**	*NS*	*0.057*	**
3	*4(5.3)*	*6(6.0)*	*1.1*	**	*NS*	*0.007*	**
4	*18(24.0)*	*20(20.0)*	*0.8*	*1.3*	*NS*	**	*0.050*
5	*2(2.7)*	*3(3.0)*	*1.1*	**	*NS*	*0.003*	**
6	*9(12.0)*	*12(12.0)*	*1.0*	**	*NS*	**	**
7	*14(18.7)*	*14(14.0)*	*0.7*	*1.4*	*NS*	**	*0.054*
8	*1(1.3)*	*3(3.0)*	*2.3*	**	*NS*	*0.017*	**
Blank	*95(126.7)*	*127(127.0)*					
total	*150(100)*	*200(100)*					
HLA- DR							
1	*8(10.7)*	*5(5.0)*	*0.4*	*2.3*	*NS*	**	*0.060*
2	*18(24.0)*	*21(21.0)*	*0.8*	*1.2*	*NS*	**	*0.038*
3	*17(22.7)*	*19(19.0)*	*0.8*	*1.2*	*NS*	**	*0.045*
4	*16(21.3)*	*20(20.0)*	*0.9*	*1.1*	*NS*	**	*0.017*
5	*3(4.0)*	*4(4.0)*	*1.0*	**	*NS*	**	**
6	*5(6.7)*	*3(3.0)*	*0.4*	*2.3*	*NS*	**	*0.038*
7	*16(21.3)*	*30(30.0)*	*1.6*	**	*NS*	*0.110*	**
8	*10(13.3)*	*9(9.0)*	*0.6*	*1.6*	*NS*	**	*0.048*
9	*6(8.0)*	*9(9.0)*	*1.1*	**	*NS*	*0.011*	**
10	*8(10.7)*	*15(15.0)*	*1.5*	**	*NS*	*0.049*	**
11	*6(8.0)*	*18(18.0)*	*2.5*	**	*NS*	*0.109*	**
12	*3(4.0)*	*6(6.0)*	*1.5*	**	*NS*	*0.021*	**
13	*7(9.3)*	*9(9.0)*	*1.0*	*1.0*	*NS*	**	*0.004*
14	*3(4.0)*	*6(6.0)*	*1.5*	**	*NS*	*0.021*	**
15	*12(16.0)*	*12(12.0)*	*0.7*	*1.4*	*NS*	**	*0.045*
52	*3(4.0)*	*8(8.0)*	*2.1*	**	*NS*	*0.042*	**
53	*3(4.0)*	*6(6.0)*	*1.5*	**	*NS*	*0.021*	**
Blank	*6(8.0)*	*0(0.0)*					
total	*150(100)*	*200(100)*					
HLA- DQ							
1	*27(36.0)*	*36(36.0)*	*1.0*	**	*NS*	**	**
2	*20(26.7)*	*36(36.0)*	*1.5*	**	*NS*	*0.127*	**
3	*25(33.3)*	*25(25.0)*	*0.7*	*1.5*	*NS*	**	*0.111*
4	*16(21.3)*	*18(18.0)*	*0.8*	*1.2*	*NS*	**	*0.041*
Blank	*62(82.7)*	*85(85.0)*					
total	*150(100)*	*200(100)*					

***=Nill*
NS= Non significant

Table 2: Antigen frequency of the HLA-class I & II of the RV patients and the cardiac control(Non RHD).

HLA antigen	Cardiac controls No.(%)	RV cases No.(%)	OR	Inverse OR	P	EF	PF
HLA-A							
1	5(14.3)	6(6.0)	0.4	2.6	NS	**	0.088
2	9(25.7)	35(35.0)	1.6	**	NS	0.125	**
3	4(11.4)	18(18.0)	1.7	**	NS	0.074	**
9	3(8.6)	6(6.0)	0.7	1.5	NS	**	0.027
10	2(5.7)	3(3.0)	0.5	2.0	NS	**	0.028
11	6(17.1)	18(18.0)	1.1	**	NS	0.010	**
23	3(8.6)	3(3.0)	0.3	3.0	NS	**	0.057
24	4(11.4)	12(12.0)	1.1	**	NS	0.006	**
25	1(2.9)	3(3.0)	1.1	**	NS	0.001	**
26	5(14.3)	15(15.0)	1.1	**	NS	0.008	**
28	6(17.1)	18(18.0)	1.1	**	NS	0.010	**
29	1(2.9)	1(1.0)	0.3	2.9	NS	**	0.019
30	4(11.4)	15(15.0)	1.4	**	NS	0.040	**
31	2(5.7)	0(0.0)	0.1	15.0	NS	**	**
32	1(2.9)	0(0.0)	0.1	8.7	NS	**	**
33	3(8.6)	27(27.0)	3.9	**	0.033	0.202	**
34	1(2.9)	3(3.0)	1.1	**	NS	0.001	**
36	0(0.0)	0(0.0)	0.4	2.8	NS	**	**
Blank	10(28.6)	17(17.0)					
total	70(100)	200(100)					
HLA-B							
5	1(2.9)	6(6.0)	2.2	**	NS	0.032	**
7	3(8.6)	6(6.0)	0.7	1.5	NS	**	0.027
8	6(17.1)	18(18.0)	1.1	**	NS	0.010	**
12	3(8.6)	3(3.0)	0.3	3.0	NS	**	0.057
13	1(2.9)	9(9.0)	3.4	**	NS	0.063	**
14	4(11.4)	9(9.0)	0.8	1.3	NS	**	0.027
15	2(5.7)	0(0.0)	0.1	15.0	NS	**	**
17	0(0.0)	6(6.0)	4.9	**	NS	0.048	**
18	0(0.0)	3(3.0)	2.5	**	NS	0.018	**
21	2(5.7)	0(0.0)	0.1	15.0	NS	**	**
22	0(0.0)	4(4.0)	3.3	**	NS	0.028	**
27	3(8.6)	3(3.0)	0.3	3.0	NS	**	0.057
35	3(8.6)	12(12.0)	1.5	**	NS	0.038	**
37	1(2.9)	8(8.0)	3.0	**	NS	0.053	**
38	0(0.0)	6(6.0)	4.9	**	NS	0.048	**
39	0(0.0)	3(3.0)	2.5	**	NS	0.018	**
40	2(5.7)	0(0.0)	0.1	15.0	NS	**	**
41	3(8.6)	6(6.0)	0.7	1.5	NS	**	0.027
44	4(11.4)	3(3.0)	0.2	4.2	NS	**	0.087
45	2(5.7)	3(3.0)	0.5	2.0	NS	**	0.028
47	0(0.0)	0(0.0)	0.4	2.8	NS	**	**
49	1(2.9)	9(9.0)	3.4	**	NS	0.063	**
50	3(8.6)	15(15.0)	1.9	**	NS	0.070	**
51	4(11.4)	9(9.0)	0.8	1.3	NS	**	0.027
52	0(0.0)	3(3.0)	2.5	**	NS	0.018	**
53	0(0.0)	3(3.0)	2.5	**	NS	0.018	**
54	0(0.0)	3(3.0)	2.5	**	NS	0.018	**
55	2(5.7)	0(0.0)	0.1	15.0	NS	**	**
56	0(0.0)	0(0.0)	0.4	2.8	NS	**	**
57	2(5.7)	6(6.0)	1.1	**	NS	0.003	**
60	2(5.7)	3(3.0)	0.5	2.0	NS	**	0.028
62	1(2.9)	3(3.0)	1.1	**	NS	0.001	**
63	0(0.0)	0(0.0)	0.4	2.8	NS	**	**
70	0(0.0)	0(0.0)	0.4	2.8	NS	**	**
73	0(0.0)	3(3.0)	2.5	**	NS	0.018	**
Blank	15(42.9)	35(35)					

total	***70(100)***	***200(100)***					
HLA-C							
1	***2(5.7)***	***3(3.0)***	***0.5***	***2.0***	***NS***	**	***0.028***
2	***3(8.6)***	***12(12.0)***	***1.5***	**	***NS***	***0.038***	**
3	***3(8.6)***	***6(6.0)***	***0.7***	***1.5***	***NS***	**	***0.027***
4	***9(25.7)***	***20(20.0)***	***0.7***	***1.4***	***NS***	**	***0.071***
5	***2(5.7)***	***3(3.0)***	***0.5***	***2.0***	***NS***	**	***0.028***
6	***6(17.1)***	***12(12.0)***	***0.7***	***1.5***	***NS***	**	***0.058***
7	***8(22.9)***	***14(14.0)***	***0.5***	***1.8***	***NS***	**	***0.103***
8	***2(5.7)***	***3(3.0)***	***0.5***	***2.0***	***NS***	**	***0.028***
Blank	***35(100.0)***	***127(127.0)***					
total	***70(100)***	***200(100)***					
HLA-DR							
1	***4(11.4)***	***5(5.0)***	***0.4***	***2.3***	***NS***	**	***0.048***
2	***6(17.1)***	***21(21.0)***	***1.3***	**	***NS***	***0.047***	**
3	***6(17.1)***	***19(19.0)***	***1.1***	**	***NS***	***0.022***	**
4	***6(17.1)***	***20(20.0)***	***1.2***	**	***NS***	***0.034***	**
5	***3(8.6)***	***4(4.0)***	***0.4***	***2.3***	***NS***	**	***0.048***
6	***1(2.9)***	***3(30)***	***1.1***	**	***NS***	***0.001***	**
7	***6(17.1)***	***30(30)***	***2.1***	**	***NS***	***0.155***	**
8	***2(5.7)***	***9(9.0)***	***1.6***	**	***NS***	***0.035***	**
9	***1(2.9)***	***9(9.0)***	***3.4***	**	***NS***	***0.063***	**
10	***2(5.7)***	***15(15.0)***	***2.9***	**	***NS***	***0.098***	**
11	***4(11.4)***	***18(18.0)***	***1.7***	**	***NS***	***0.074***	**
12	***3(8.6)***	***6(6.0)***	***0.7***	***1.5***	***NS***	**	***0.027***
13	***1(2.9)***	***9(9.0)***	***3.4***	**	***NS***	***0.063***	**
14	***1(2.9)***	***6(6.0)***	***2.2***	**	***NS***	***0.032***	**
15	***9(25.7)***	***12(12.0)***	***0.3***	***3.4***	***NS***	**	***0.221***
52	***1(2.9)***	***8(8.0)***	***3.0***	**	***NS***	***0.053***	**
53	***1(2.9)***	***6(6.0)***	***2.2***	**	***NS***	***0.032***	**
Blank	***13(37.1)***	***0(0.0)***					
total	***70(100)***	***200(100)***					
HLA-DQ							
1	***14(40.0)***	***36(36.0)***	***0.8***	***1.2***	***NS***	**	***0.063***
2	***9(25.7)***	***36(36.0)***	***1.6***	**	***NS***	***0.138***	**
3	***10(28.6)***	***25(25.0)***	***0.8***	***1.2***	***NS***	**	***0.048***
4	***7(20.0)***	***18(18.0)***	***0.9***	***1.1***	***NS***	**	***0.024***
Blank	***30(85.7)***	***85(85.0)***					
Total	***70(100)***	***200(100)***					

= Nill NS= Non significant

Table 3 : Literature data shows the association of HLA phenotype of RF and RHD in different ethnic groups

Publication	***Decreased frequency***	***Increased frequency***	***Country***
Ayoub *e al*., 1986(6)		DR2,DR4	U.S.A
Cauphey *et al*.,1975(7)	A10	A3,B8	Maoris
	A28	B17	Europeans
Jhinphan *et al*.,1986(10)	DR2	DR3,A33	North Indian
Leirisalo *et al*., 1977(11)		B35	Finnish
Goriaeva and Benevolenskaia,1986 (12)		A11,B27,Cw2,Cw3,DR5,DR7	USSR
Guedez, 1999 (13)		DR6, DR7, DQ2	Egypt
Donadi *et al.,* 2000 (14)		B4,DR1	Brazil
Olmez *et al*.,1992(16)	A10,B35	DR11(with carditis)	Turkey
Present Study	A1	A33	Iraq

Table 4: Status of ABO blood groups in RV patients as compared to controls.

	Study groups			
	Healthy controls No.(%)	*Non RHD controls No.(%)*	*Rheumatic Valvulitis cases No.(%)*	*P value*
Blood groups **A**	**27(36)**	**19(54.3)**	**33(33)**	**NS**
B	**16(21.3)**	**5(14.3)**	**36(36)**	**0.04**
AB	**13(17.3)**	**2(5.7)**	**9(9)**	**NS**
O	**19(25.3)**	**9(25.7)**	**22(22)**	**NS**
Total	**75 (100)**	**35 (100)**	**100(100)**	

Table 5 : Association of HLA-A33 with blood groups antigens in RV patients as compared to controls.

	Total *No.* *(%)*	*HLA-A33 antigen* *No* *(%)*	*P*
Healthy controls **Blood group** **A**	**27 (36)**	**3 (11.1)**	**NS**
B	**16 (21.33)**	**1 (6.3)**	**NS**
AB	**13 (17.33)**	**2 (15.4)**	**NS**
O	**19 (25.33)**	**1 (5.3)**	**NS**
Total	**75**	**7**	
Cardiac controls**(non RHD)** **Blood group** **A**	**19 (54.28)**	**1 (5.3)**	**NS**
B	**5 (14.28)**	**1 (20.0)**	**NS**
AB	**2 (5.71)**	**1 (50.0)**	**NS**
O	**9 (25.71)**	**0 (0.0)**	**NS**
Ttotal	**35**	**3**	
Rheumatic Valvulitis cases **Blood group** **A**	**33 (33)**	**0 (0.0)**	**NS**
B	**36 (36)**	**24 (66.7)**	**<0.001**
AB	**9 (9)**	**0 (0.0)**	**NS**
O	**22 (22)**	**3 (13.6)**	**NS**
Total	**100**	**27**	

Discussion:

The role of genetic factors in the etiology of rheumatic heart disease was documented many decades ago .As a result ,the investigative efforts were focused on the genetic markers of susceptibility to this preventable disease. These studies have been influenced by the accumulation of data about the importance of HLA in the immune response. In view of an abnormal auto immune response exhibited by the RF/RHD patients, the HLA region has been under scrutiny for markers of susceptibility.

In the present work, there was significant association of HLA-A33 with RV patients [P=(0.005),(0.033)] as compared with healthy and cardiac control respectively. This result in agreement with that of Jhinphan *et al*.,(1986)(10) regarding significant statistical results of A33 Ags as compared with control group,but disagreed with result of the workers (11, 12, 13,14) table(3). In addition, the A1-Ag showed significant low frequency in RV patient when compared with healthy control (PF=0.177) and there was no significant differences as compared with cardiac control so, A1-Ag may has protective value, this finding was not consistant with that of Falk *et al*., (1973)(15) ; Cauphey *et al*., (1975)(7); and Olmez *et al*., (1992)(16) about the type of protective Ag .

❖ As shown in table (3) the frequency of class I and class II HLA-Ag showed conflicting results in patients with RHD by different authores. The reason for these discrepancies are probably related to:

* Although DR4 associated genetic predisposition has been suggested for RHD, other studies failed toconfirm this.The disparity may be due to antisera

not being monospecific and thereby increasing the cross reactivity in the control group (17). (recently monoclonal Abs have been used which are more sensitive and more specific).

** Ethnic differences must also taken into account. The frequency of a particular allele in one population can be very different from that in another population. The reason of race variation is not clearly known. It may be due to gene drift or gene flow due to admixture between different populations (18).

*** Different rheumatogenic strain of streptococcus pyogenes in different countries may be explain the differences in type of specific HLA-Ag which associated with RV patients in different nations. i.e the molecular mimicry between specific HLA-Ag with certain rheumatogenic strain predispose to occurrence of autoimmunity in predisposing individual, so identification of rheumatogenic strain of streptococcus is important to have an idea about susceptibility to RV.

Significant increase in the frequency of blood group B in RV patients as compared to control groups (P=0.04) was showed in the current work. Also Ali, (1989)(19) found significant increase in the frequency of blood group B in Iraqi patients with RHD. Aswellas, an interesting observation was a strong association of blood group B with A33-Ag among RV patients (P<0.001).Such association have proved the utility of HLA and blood group antigens as useful tool in understanding the susceptibility and pre-disposition of individuals to RHD. This phenomena, may indicate the presence of at least one important genetic factor for susceptibility to RV disease.

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