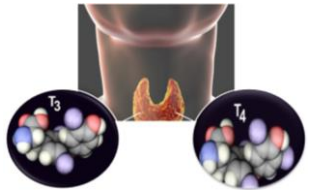

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Prevalence and Frequency Distribution of HLA-A, HLA-B and HLA-C Alleles in the Punjab, Pakistan

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ABSTRACT: *The Human Leukocyte Antigen (HLA) system, a set of highly polymorphic genes, has been found to play an effective role in the disease resistance and disease susceptibility. In this study, prevalence of class-I alleles of HLA was characterized at HLA-A,-B and -C loci in the 216 individuals randomly selected population at different regions of Punjab province of Pakistan. The study revealed that at HLA-A locus the allele 11 was most prevalent with 16.7 % frequency. Similarly, at HLA-B locus the allele 51 was found abundant with 15% frequency and at HLA-C locus the allele 7 was prevalent with 24% frequency. Among the two-locus HLA class I haplotypes, B*08/C*07 was found to be the most prevalent followed by B*35/C*04. Surprisingly, HLA-B*29 and HLA-B*36 alleles were found in the Punjabi population which is contrary to the previous reports.*

Keyword: *Allele frequency, HLA, MHC-I, Pakistan*

INTRODUCTION

Major histocompatibility complex (MHC), human leukocyte antigen (HLA), consists of genes which are highly polymorphic and play significant role in immune response, especially in adaptive immune system. These genes encode proteins that are involved in foreign organ rejection (Stephen and John, 2000). The region of HLA spans 3600 kbp on the chromosome 6 (Terasaki, 1990). The HLA is further divided into two classes: HLA-A, -B and –C have been placed under class I, while HLA-DR,-DQ and –DP have been placed under class II.

On cell surface, MHC proteins are expressed endogenously and exogenously to discriminate between self and nonself-antigens through adaptive immune response (Harjanto et al., 2014) . Molecules of HLA class-I present the cytosolic intracellular peptides to the CD8+ cytotoxic T cell receptors that kill the infected cells directly (Ghodke et al., 2005; Suheir and Amos, 2014) (Carapito et al., 2016). HLA class-I molecules help in recognition and binding of intracellular peptides and present these intracellular peptides to the cytotoxic T-cells while extracellular peptides are recognized by HLA class II molecules which present them to the helper T-cells. Earlier researches on transplant failure have revealed the importance of HLA variability complex to induce adaptive immunity (Billerbeck et al., 2013; King et al., 2002; Reiher et al., 2017)

HLA individual alleles are responsible for susceptibility and prevention from autoimmune and infectious diseases. Previous studies reveal that these alleles are associated with different infectious and autoimmune diseases so the prevalence of an allele can help to predict the susceptibility of a disease in the studied population (Ghodke et al., 2005; Howell, 2014). Due to its extreme polymorphic nature, the frequency of HLA alleles can vary among different populations and hence this can provide important information about susceptible of a given population towards diseases. HLA genetic variability occurs due to alterations in

the alleles of HLA genes. HLA antigens are the proteins recognized by the immune system of host during organ transplantation, blood transfusion and pregnancy (Reiher et al., 2017)

Pakistan possesses great diversity among its civilization and ethnicity (Blood, 1996). Major ethnic groups include Punjabi, Sindhi, Saraikis, Pashtuns, Baloch, Muhajir, Pathan, Hindkowans, Rajputs and Chitralis (Mushtaq, 2009). Punjab is the most populous province of Pakistan with an estimated population of about 30.4 million belonging to various ethnic groups (Ahmed, 1990).

The study of HLA has been conducted in various countries of the world in the recent past that has ultimately helped in prevention of several diseases (Abedini et al., 2021). In this study, the distribution of HLA alleles was determined in 216 unrelated individuals from different divisions of Punjab based upon geographical distribution. The purpose of this study was to explore the diversity of HLA class I alleles among the Punjabi population for the establishment of a reference data set for further studies such as HLA and its association with chronic diseases.

MATERIALS AND METHODS

For HLA genotyping, blood sample of 216 healthy individuals was taken which were randomly selected from different regions of Punjab. DNA extraction was done from whole blood sample using salting out method. Briefly, proteinase K and lysis buffer containing SDS were used for lysing cells. Afterwards, supernatant was treated with Phenol-chloroform-

isoamyl alcohol. The process was repeated to completely remove the RBCs. At the end the, salting out method was applied for DNA isolation .PCR sequence specific priming (SSP) was used for typing HLA-A, -B and –C alleles according to manufacturer's instructions (One Lambda, Inc., USA). For calculating allele frequencies, we used direct counting method (No of copies of alleles /2n in the sample population) (González-Galarza et al., 2015). Gene frequencies were calculated using the formula;$(GF = 1 - \sqrt{1 - AF})$ (Kaštelan, 1991). Hardy Weinberg law was applied for the calculation of haplotype frequencies (Serre, 1997)

RESULTS

It was observed that our studied population contained 54 HLA class I alleles 27 HLA-A, 14 HLA-B and 13 HLA-C alleles. Allele frequencies obtained from HLA class I alleles has been described in Table 1.

It was noted that for HLA class-I A locus, allele A*11, A*02 and A*01 were the most common; at locus B allele B*51, B*01 and B*40 were the most common, whereas, at locus C allele C*07, C*06 and C* were the most prevalent.

Table 1: Allele frequency of HLA Class 1

Alleles n=216	AF (%)	GF (%)	Alleles n=216	AF (%)	GF (%)	Alleles n=216	AF (%)	GF (%)
A*01	12.3	6.351722	B*07	3.9	1.969393	C*01	3.2	1.613009
A*02	15.3	7.967397	B*08	14.6	7.58788	C*02	0.9	0.451017
A*03	9.8	5.026319	B*13	3.2	1.613009	C*03	6.9	3.511659
A*11	16.7	8.731166	B*14	0.7	0.350615	C*04	10.8	5.554248
A*23	1.4	0.702467	B*15	5.6	2.840338	C*05	1.4	0.702467
A*24	7.6	3.875081	B*18	1.9	0.954556	C*06	13.6	7.0484
A*26	9.5	4.868512	B*27	1.6	0.803226	C*07	24	12.82202
A*29	1.4	0.702467	B*29	0.2	0.10005	C*08	3.2	1.613009
A*30	0.9	0.451017	B*35	10.2	5.237138	C*12	10.8	5.554248
A*31	4.4	2.224748	B*36	0.2	0.10005	C*14	6.2	3.1496
A*32	5.6	2.840338	B*37	2.3	1.15669	C*15	12.9	6.672619
A*33	7.4	3.771106	B*38	0.5	0.250313	C*16	4.2	2.122526
A*68	6.9	3.511659	B*39	1.4	0.702467	C*17	1.1	0.551521
A*74	0.2	0.10005	B*40	10.9	5.607204			
			B*41	0.9	0.451017			
			B*44	4.9	2.480771			
			B*45	0.9	0.451017			
			B*48	0.9	0.451017			
			B*49	0.7	0.350615			
			B*50	4.6	2.327076			
			B*51	15	7.804555			
			B*52	5	2.532057			
			B*53	0.4	0.2002			
			B*55	1.9	0.954556			
			B*56	0.2	0.10005			
			B*57	4.6	2.327076			
			B*58	2.5	1.257912			

Different haplotypes of HLA class I (Haplotype A/B, A/C and B/C) have been shown in Table 2.

Table 2: Most prevalent HLA class I haplotypes (A/B, A/C and B/C) in Punjab population of Pakistan

A*02/B*40	3.937	A*11/C*07	4.839	B*08/C*07	8.469
A*26/B*08	3.937	A*26/C*07	4.839	B*35/C*04	5.22
A*11/B*07	3.6	A*02/C*15	3.687	B*40/C*15	4.292
A*11/B*51	2.925	A*01/C*07	3.226	B*51/C*14	3.596
A*03/B*35	1.8	A*33/C*07	2.88	B*51/C*07	3.364
A*31/B*51	1.8	A*02/C*07	2.65	B*51/C*15	3.248
A*01/B*51	1.687	A*11/C*06	2.535	B*50/C*06	3.016
A*11/B*08	1.687	A*01/C*06	2.419	B*57/C*06	2.9
A*11/B*35	1.687	A*02/C*06	2.304	B*52/C*12	2.32
A*11/B*40	1.687	A*11/C*12	2.189	B*44/C*07	2.204
A*11/B*44	1.687	A*11/C*15	1.959	B*40/C*07	1.972
A*02/B*51	1.575	A*03/C*06	1.843	B*15/C*06	1.74
A*26/B*51	1.575	A*01/C*15	1.728	B*07/C*07	1.508
A*68/B*51	1.575	A*03/C*12	1.728	B*40/C*12	1.508
A*01/B*08	1.462	A*11/C*04	1.728	B*08/C*12	1.392
A*02/B*08	1.462	A*02/C*03	1.613	B*37/C*06	1.392
A*01/B*57	1.35	A*01/C*12	1.498	B*07/C*15	1.276
A*03/B*50	1.237	A*03/C*04	1.382	B*40/C*03	1.276
A*03/B*51	1.237	A*03/C*07	1.382	B*58/C*03	1.276
A*11/B*57	1.237	A*11/C*03	1.382	B*08/C*15	1.16
A*33/B*08	1.237	A*24/C*07	1.382	B*13/C*06	1.16
A*01/B*40	1.125	A*31/C*14	1.382	B*15/C*03	1.16
A*24/B*40	1.125	A*24/C*15	1.267	B*52/C*07	1.16
A*02/B*15	1.012	A*33/C*04	1.267	B*35/C*07	1.044
A*03/B*08	1.012	A*02/C*04	1.152	B*39/C*12	1.044
A*68/B*08	1.012	A*24/C*04	1.152	B*51/C*16	1.044
A*01/B*07	0.9	A*32/C*04	1.152	B*13/C*04	0.928
A*01/B*15	0.9	A*68/C*15	1.152	B*15/C*07	0.928
A*01/B*35	0.9	Av02/C*12	1.037	B*35/C*06	0.928
A*01/B*52	0.9	A*32/C*07	1.037	B*08/C*04	0.812
A*02/B*50	0.9	A*68/C*07	1.037	B*35/C*12	0.812
A*02/B*57	0.9	A*24/C*12	0.922	B*44/C*05	0.812
A*11/B*52	0.9	A*33/C*03	0.922	B*51/C*06	0.812

A*24/B*35	0.9	A*68/C*04	0.922	B*51/C*12	0.812
A*24/B*51	0.9	A*01/C*04	0.806	B*55/C*01	0.812
A*32/B*35	0.9	A*02/C*14	0.806	B08/C14	0.696
A*33/B*35	0.9	A*26/C*04	0.806	B*08/C*16	0.696
A*33/B*44	0.9	A*26/C*12	0.806	B*18/C*07	0.696
A*68/B*35	0.9	A*31/C*07	0.806	B*41/C*17	0.696

The prevalence of HLA-A, -B and –C frequencies in Punjab population in comparison to human populations belonging to Italy, Jordan, Brazil, China, Syria, France, Sudan and Lebanon has been described in Table 3 and Table 4.

Table 3: HLA-A Allele frequencies in Punjab population of Pakistan compared to other countries.

Allele	Pakistan (n=216)	Italy (n=500)	Jordan (n=15141)	Brazil (n=1559)	China (n=26266)	Syria (n=105)	France (n=130)	Sudan (n=250)	Lebanon (n=1994)
A*01	0.123	0.121	0.150	0.103	0.024	0.129	0.277	0.168	0.230
A*02	0.153	0.254	0.123	0.249	0.313	0.190	0.423	0.484	0.405
A*03	0.098	0.114	0.088	0.082	0.019	0.129	0.246	0.176	0.250
A*11	0.167	0.060	0.041	0.050	0.226	0.030	0.085	0.072	0.105
A*23	0.014	0.025	0.039	0.053	0.002	0.030	0.023	0.076	0.065
A*24	0.076	0.122	0.104	0.095	0.173	0.131	0.200	0.172	0.205
A*26	0.095	0.050	0.044	0.036	0.026	0.036	0.085	0.040	0.070
A*29	0.014	0.036	0.030	0.049	0.007	0.030	0.108	0.024	0.065
A*30	0.009	0.050	0.087	0.064	0.060	0.090	0.077	0.220	0.080
A*31	0.044	0.025	0.017	0.042	0.036	0.052	0.092	0.048	0.015
A*32	0.056	0.051	0.035	0.038	0.009	0.010	0.138	0.064	0.055
A*33	0.074	0.022	0.035	0.027	0.089	0.052	0.046	0.032	0.040
A*68	0.069	0.000	0.048	0.062	0.005	0.071	0.108	0.120	0.000
A*74	0.002	0.000	0.008	0.012	0.000	0.000	0.000	0.024	0.000

Table 4: HLA-B Allele frequencies in Punjab population of Pakistan compared to other countries.

Allele	Pakistan (n=216)	Italy (n=500)	Jordan (n=15141)	Brazil (n=1559)	China (n=26266)	Syria (n=106)	France (n=130)	Sudan (n=250)	Lebanon (n=1309)
B*07	0.039	0.056	0.032	0.0631	0.018	0.043	0.146	0.084	0.085
B*08	0.146	0.059	0.023	0.0496	0.007	0.048	0.169	0.064	0.045
B*13	0.032	0.034	0.028	0.0144	0.105	0.033	0.038	0.048	0.065
B*14	0.007	0.036	0.041	0.0589	0.0009	0.062	0.092	0	0.043
B*15	0.056	0	0.049	0.0871	0.15	0.024	0.154	0	0.029
B*18	0.019	0.048	0.046	0.0564	0.003	0.048	0.092	0.048	0.075
B*27	0.016	0.019	0.016	0.0176	0.031	0.024	0.062	0.028	0.03
B*29	0.002	0	0	0	0	0	0	0	0
B*35	0.102	0.159	0.141	0.1208	0.043	0.186	0.154	0.112	0.355
B*36	0.002	0	0	0	0	0	0	0	0
B*37	0.023	0.014	0.009	0.0105	0.01	0.01	0.062	0.032	0.01
B*38	0.005	0.035	0.042	0.0269	0.027	0.057	0.038	0.068	0.07
B*39	0.014	0.027	0.014	0.0275	0.028	0.01	0.046	0.132	0.005
B*40	0.109	0.026	0.022	0.0423	0.159	0.024	0.115	0	0.035
B*41	0.009	0.013	0.057	0.0141	0.0008	0.01	0.031	0.156	0.105
B*44	0.049	0.092	0.061	0.1057	0.025	0.076	0.262	0.028	0.135
B*45	0.009	0.004	0.021	0.0134	0.002	0.019	0.031	0.032	0.035
B*48	0.009	0.000	0	0.0051	0.0191	0	0	0.012	0
B*49	0.007	0.035	0.067	0.0285	0.0008	0.057	0.054	0.08	0.085
B*50	0.046	0.018	0.066	0.0214	0.004	0.019	0.023	0.104	0.04
B*51	0.15	0.104	0.099	0.0863	0.068	0.081	0.115	0.176	0.155
B*52	0.05	0.014	0.046	0.0176	0.027	0.071	0.023	0.1	0.07
B*53	0.004	0.008	0.025	0.0266	0.0004	0.03	0.031	0.06	0
B*55	0.019	0	0.019	0.0096	0.03	0.024	0.062	0.008	0.045
B*56	0.002	0	0.002	0.0041	0.005	0	0	0.004	0
B*57	0.046	0	0.029	0.0387	0.01	0.005	0.069	0.116	0.015
B*58	0.025	0	0.025	0.025	0.068	0.014	0.031	0.028	0.025

DISCUSSION

Our results suggested high diversity of HLA class I alleles in Punjab population of Pakistan. Previous studies suggest that allele HLA-A*02 is higher in prevalence at HLA–A

locus in the human population throughout the world (Clayton and Lonjou, 1997), however in our studies we found that allele HLA-A*11 with 16.7% was the most prevalent in the studies population. Moreover, prevalence of HLA-A*11 was intermediate when compared with other human populations. The human populations of Italy, Brazil, China, Syria, France and Sudan indicated that the most prevalent allele is HLA-A*03, whereas in our studies population allele HLA-A*03 was second in prevalence (Ayo et al., 2015; Dafalla et al., 2014; Du et al., 2007; Dubois and Gebuhrer, 2004; Ikhtiar et al., 2018; Rendine et al., 1998). In addition allele HLA-A*01 is third in prevalence in population which is consistent with human populations of Italy and France (Du et al., 2007; Dubois and Gebuhrer, 2004). It was interesting to notice that allele HLA-A*74 which was least common in our population was also found least common in human populations of Jordon, Brazil and Japan (Ayo et al., 2015; Du et al., 2007). However, some other studies showed that it was not observed in human populations of Italy, China, Syria, France and Lebanon (Dafalla et al., 2014; Du et al., 2007; Dubois and Gebuhrer, 2004; Elbjeirami et al., 2013; Ikhtiar et al., 2018).

For B locus of HLA, it was found that the most prevalent alleles in our cohort study (prevalence >10 %) were HLA-B*51, HLA-B*08, HLA-B*40 and HLA-B*35. HLA-B*51 was the most prevalent in our sample population while the most prevalent allele in human population of Italy, Jordan, Brazil and Syria was HLA-B*35 (Ayo et al., 2015; Elbjeirami et al., 2013; Ikhtiar et al., 2018; Rendine et al., 1998). However, HLA-B*51 was second in prevalence in human population of Italy, Jordan and Syria. Interestingly, it was noted that the second most prevalent allele in our sample population HLA-B*08 was lower in prevalence in our studied cohort, except in France (Ayo, C.M. et al., 2015; Dafalla et al., 2014; Du et

al., 2007; Dubois & Gebuhrer, 2004; Elbjeirami et al., 2013; Ikhtiar et al., 2018; Rendine et al., 1998; Salti and Shaya, 1997a). Moreover, our study also indicated that the allele HLA-B*29 and HLA-B*36 found in our studied population were not present in our compared cohort population.

For HLA-C locus, it was found that HLA-C*07 was the most abundant allele in our sample population with 12.8 % prevalence, while HLA-C*02 was the least prevalent allele with 0.9 % prevalence in our sample population. When two-locus haplotype frequency was determined in the sample population, it was found that B*08/C*07 was the most prevalent, which is also the most prevalent haplotype around the world, whereas, B*35/C*04 was found to be second in prevalence which is consistent with the Syrian population studies. Moreover these frequent haplotypes have also been found predominant in Mediterranean populations such as: Europeans (Nunes et al., 2014), Iranians (Abroun and Farzanehkhah, 2010) and Lebanese (Salti and Shaya, 1997b).

CONCLUSION

Allelic prevalence and frequency determination at different HLA loci help finding compatible HLA match individuals. Knowledge of association of various alleles with different diseases can also help avoiding the onset of certain diseases. The study indicated that allele HLA-A*11 with 16.7% was the most prevalent in the studied population. At HLA locus B, HLA-B*51 was the most prevalent in our sample population, For HLA-C locus, it was found that HLA-C*07 was the most abundant allele in our sample population.

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