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Distribution of HLA (Class I and Class II) antigens in the native Dravidian Hindus of Tamil Nadu, South India

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SUMMARY

HLA - A, B, C, DR, DQ antigen profile of South Indian Tamil-speaking Hindus of Dravidian descent was studied. Phenotype. gene and haplotype frequencies were calculated and compared with the literature. There was a complete lack of A23, A25 and A32 antigens in the sample presently monitored. Except for minor differences (higher incidence of Cw6 and DR10 antigens), the Dravidian Hindus show similarity to North Indio-Aryan and other Hindu samples. The haplotypes A1, B17; A2, B5: A2, B51; A1, DR7; B12, DR7; B13, DR2; B17, DR7; DR2, DQ1; DR3, DQ2; DR4, DQ3; DR5, DQ3; DR7, DQ2; DR11, DQ3 show significant positive linkage disequilibrium whereas A1, DR2; DR2, DQ2; DR7, DQ1 were significant for negative linkage disequilibrium in the Dravidian Hindus.

INTRODUCTlON

The vast Indian subcontinent lies between 8°N and 37°N latitude and 68°E and 97°E longitude. The Indian population can be divided broadly into Dravidians and Aryans. The Dravidians, the original inhabitants of India, migrated southwards after the invasion of North India by the Aryans from the Iranian plateau. The Dravidians, distributed in the southern states of India, are regarded as dark-skinned Caucasoids [Coon 1983]. The South Indian Hindus of this descent represent a large endogamic ethnic group of the Indian subcontinent [Mittal *et al* 1982].

Initial studies on the HLA antigen distribution among the different Indian population groups were carried out on Indian migrants co foreign countries

[Brain and Hammond 1972; Singal 1972; Ting and Morris 1972; Hammond *et al* 1975; Hammond and Asmal 1980; Suciu-Foca *et al* 1981; Mittal *et al* 1982]. Subsequently, regional studies carried out on native Indians have also been reported [Raha 1975; Bale *et al* 1980; Verma *et al* 1983; Pitchappan *et al* 1984; Mehra *et al* 1986; Selvakumar *et al* 1988]. It has been suggested that the populations in the eastern regions are closer to Mongoloids [Festenstein *et al* 1972] while those in the western regions are closer to Caucasoids [Solheim *et al* 1972].

In recent years, HLA studies on some endogamous groups including few castes and tribals have also been published [Wadia *et al* 1980; Papiha *et al* 1983, 1989; Pitchappan *et al* 1984; Rajashekar *et al* 1987; Selvakumar *et al* 1987]. However, considering the enormous diversity among Indian populations, the available information is inadequate; furthermore most of the studies were restricted mainly to HLA class I antigens [Papiha and Mastana 1990]. It was therefore felt worthwhile to study the HLA class I and class II antigen profiles in the South Indian Hindus (Dravidians) living in and around Madras, the capital city of Tamil Nadu State and compare the data with those of the North Indian Hindus (Aryans).

MATERIALS AND METHODS

A total of 113 unrelated, healthy Tamil-speaking Hindus (mostly students and researchers) residing in and around Madras city formed the sample. for the study.

HLA typing - Peripheral blood lymphocytes were separated from heparinized blood samples using Ficoll-Hypaque density gradient as described elsewhere [Boyum 1968]. The antisera used for class I typing were from NIH USA (83 sera) and from cooperative HLA laboratories in India (30 sera); 10 well established sera of local origin [Selvakumar *et al* 1985; Subramanian *et al* 1992a] were also included. For DR and DQ, 28 sera from cooperative HLA laboratories in India and 5 well established sera of local origin [Subramanian *et al* 1992b] were employed. The typing tray contained at least two antisera for each specificity. HLA-A, B and C antigens were determined by two-stage microlymphocytotoxicity test [Terasaki and McClelland 1964]. For DR and DQ typing, the test was carried out with longer incubation period5, utilizing nylon wool column separated B-lymphocytes [Werner *et al* 1977; Subramanian *et al* 1992b].

Statistical analysis - Phenotype frequency (PF), gene frequency (GF), standard error of gene frequency (SEGF), haplotype frequency (HF), linkage disequilibrium (A) and t-values were calculated as described by Mittal [1976]. Gene frequencies for each locus are estimated by the square root method, therefore they do not sum up to 1.

Table I - Phenotype frequency (PF) and gene frequency (GF) of HLA - A, B, C antigens in South Indian (Tamil Nadu) Hindus of Dravidian descent (N = 113).

Antigen	% PF	% GF	SE GF
A1	38.9	21.9	3.1
A2	37.2	20.7	3.0
A3	15.9	8.3	1.9
A9	38.1	21.3	3.1
A23 (<A9)	0.0	0.0	0.0
A24 (<A9)	28.3	15.3	2.6
A10	8.0	4.1	1.3
A25 (<A10)	0.0	0.0	0.0
A26 (<A10)	5.3	2.7	1.1
A l l	24.8	13.3	2.4
A19	18.6	9.8	2.1
A29 (<A19)	1.8	0.9	0.6
A30+31 (<A19)	7.1	3.6	1.3
A32 (<A19)	0.0	0.0	0.0
A33 (<A19)	9.7	5.0	1.5
A28	4.4	2.3	1.0
A -	14.2	7.3	1.8
B5	37.2	20.7	3.0
B51 (<A5)	23.9	12.8	2.4
B52 (<B5)	0.9	0.4	0.4
B7	16.8	8.8	2.0
B8	5.3	2.7	1.1
B12	11.5	5.9	1.6
B44 (<B12)	9.7	5.0	1.5
B13	14.2	7.3	1.8
B14	1.8	0.9	0.6
B15	9.7	5.0	1.5
B62 (<B15)	7.1	3.6	1.3
B17	30.1	16.4	2.7
B21	0.9	0.4	0.4
B22	10.6	5.5	1.6
B27	0.9	0.4	0.4
B35	13.3	6.9	1.7
B40	25.7	13.8	2.5
B -	22.1	11.8	2.3
Cw1	8.0	4.1	1.3
Cw2	4.4	2.3	0.9
Cw3	12.4	6.4	1.6
Cw4	26.5	14.3	2.4
Cw5	6.2	3.1	1.2
Cw6*	32.0	17.5	4.0
Cw-	10.5	5.5	1.6

* N = 5 0

Table II - Phenotype frequency (PF) and gene frequency (GF) of HLA-DR and DQ antigens in South Indian (Tamil Nadu) Hindus of Dravidian descent (N = 113).

Antigen	% PF	% GF	SE GF
DR1	8.0	4.1	1.3
DR2	47.8	27.7	3.5
DR3	17.7	9.3	2.0
DR4	18.6	9.8	2.1
DR5	23.9	12.8	2.4
DR11 (<DR5)	4.4	2.2	1.0
DR6*	16.0	8.3	2.8
DR7	37.2	20.7	3.0
DR8*	11.4	5.7	2.0
DR9*	3.2	2.0	1.1
DR10*	14.3	7.4	2.4
DR-	1.8	0.2	0.6
DR52	76.1	51.1	4.0
DR53	44.2	25.3	3.1
DR-	79.6	54.9	4.2
DQ1	76.1	51.1	4.8
DQ2	42.5	24.0	3.0
DQ3	49.5	29.0	3.3
DQ-	31.9	17.5	2.7

*N=50

RESULTS AND DISCUSSION

The percent phenotype and gene frequencies of HLA - A, B, C (class I) and HLA - DR, DQ (class 11) antigens observed among the South Indian Tamil Hindus of Dravidian descent are presented in Tables I and II respectively. A23, A25 and A32 antigens were not found in the present sample of 113 individuals. However, low incidence of A28, A29, B52, B14, B21, B27, Cw2, DR11 and DR9, and, high frequencies of A1, A2, A9, A11, B5, B17, B40, Cw4, Cw6, DR2, DR5, DR7, D52, DR53, DQ1, DQ2 and DQ3 have been noted.

Table III shows a comparison of the gene frequency data of the presently monitored native Tamil-speaking Dravidian Hindus with the literature reported on HLA profiles of Indian Hindus (native South/South elsewhere; native North/North elsewhere; pooled). Relatively higher gene frequencies of Cw6 and DR10 were noted as minor differences from the other Indian Hindu groups. Nevertheless the overall HLA distribution reveals the commonness among Indians, irrespective of their region and of whether the groups are indigenous or not.

Table III - HLA gene frequencies in native South Indian (Tamil Nadu) Hindus of Dravidian descent compared to other Hindu samples.

HLA allele	Native South Indian (Tamil Nadu) Dravidian Hindus	Native South Indian Tamil Hindus	Native South Indians (Madurai)	South Indian Tamil Hindus (S. Africa)	South Indian Dravidian Hindus (S. Africa)	Native North Indian Aryan Hindus	Native North Indian Hindus Lucknow)	North Indian Aryan Hindus (S. Africa)	North Indian Aryan Hindus (S. Africa)	South & North Indian Hindus (USA)
	N = 113	N = 240	N = 385	N = 288	N = 424	N = 400	N = 59	N = 193	N = 208	N = 138
	(a)	(b)	(c)	(d)	(e)	(f)	(g)	(d)	(e)	(h)
A1	21.9	22.1	13.1	16.7	18.0	14.5	14.6	9.8	9.9	20.6
A2	20.7	18.3	16.4	16.7	19.0	11.9	16.6	13.6	13.7	10.3
A3	8.3	7.1	6.3	8.0	7.0	8.9	15.6	7.5	7.8	7.1
A9	21.3	14.1	16.7	NT	NT	14.5	NT	NT	NT	14.0
A23	0.0	NT	NT	NR	0.5	NT	0.0	NR	0.0	0.4
A24	15.3	1.2	NT	15.9	13.0	NT	15.6	17.3	16.8	13.6
A10	4.1	3.3	3.4	NT	NT	5.4	NT	NT	NT	2.9
A25	0.0	NT	NT	NR	1.0	NT	0.0	NR	1.2	0.0
A26	2.7	0.4	NT	4.1	3.4	NT	1.7	3.1	3.0	2.9
A11	13.3	14.2	16.6	13.4	14.0	13.8	18.7	16.7	17.1	14.5
A19	9.8	3.1	11.6	NT	NT	18.4	NT	NT	NT	NT
A29	0.9	NT	NT	NR	0.4	2.1	0.0	NR	1.0	1.5
A30+31	3.6	NT	NT	NR	3.4	5.6	7.8	NR	4.8	3.0
A32	0.0	0.0	NT	1.0	1.3	5.0	0.0	1.6	1.5	2.9
A33	5.0	0.0	NT	3.7	3.9	2.0	NT	2.9	3.7	12.0
A28	2.3	4.6	6.5	7.2	6.5	7.9	2.6	9.8	9.6	6.0
A-	7.3	11.2	8.9	16.0	15.7	NR	6.8	18.3	17.7	4.9
B5	20.7	14.4	18.1	21.1	19.1	16.0	NT	20.2	18.6	14.9
B51	12.8	0.8	NT	11.0	12.0	NT	3.5	8.9	12.6	7.5
B52	0.4	NT	NT	5.4	4.0	NT	2.6	7.8	4.4	6.4
B7	8.8	7.9	10.1	8.1	7.9	6.5	14.6	3.9	3.7	3.7
B8	2.7	2.9	1.8	3.0	3.0	4.4	4.3	2.6	2.5	3.7
B12	5.9	5.0	5.3	NT	NT	9.0	NT	NT	NT	10.7
B44	5.0	NT	NT	4.8	4.0	7.5	18.7	10.7	10.4	10.3

Table III - (cont.)

HLA allele	Native South Indian (Tamil Nadu) Dravidian Hindus	Native South Indian Tamil Hindus	Native South Indians (Madurai)	South Indian Tamil Hindus (S. Africa)	South Indian Dravidian Hindus (S. Africa)	Native North Indian Aryan Hindus	Native North Indian Hindus Lucknow)	North Indian Aryan Hindus (S. Africa)	North Indian Aryan Hindus (S. Africa)	South & North Indian Hindus (USA)
	N = 113	N = 240	N = 385	N = 288	N = 424	N = 400	N = 5 9	N = 193	N = 208	N = 138
	(a)	(b)	(c)	(d)	(e)	(f)	(g)	(d)	(e)	(h)
B13	7.3	3.8	3.0	3.2	4.0	4.0	0.9	2.6	2.5	3.3
B14	0.9	1.9	0.1	0.0	0.0	0.0	1.7	0.5	1.0	0.4
B15	5.0	4.0	5.9	5.0	5.2	6.9	0.9	6.7	6.5	8.3
B62	3.6	NT	NT	NT	NT	5.4	NT	NT	NT	3.3
B16	NT	0.0	0.4	1.1	1.0	1.1	0.9	1.1	1.3	2.2
B17	16.4	10.2	10.1	12.2	12.0	7.8	12.7	8.7	9.4	
B18	NT	0.8	0.5	0.7	1.0	2.2	4.3	2.6	3.0	2.6
B21	0.4	0.0	2.8	0.9	1.0	3.3	0.0	1.1	1.0	14.0 0.7
B22	5.5	5.0	2.5	1.4	1.5	2.9	0.0	0.8	1.0	1.1
B27	0.4	1.0	0.9	0.0	1.0	3.0	0.8	2.9	2.7	0.7
B35	6.9	9.1	10.3	9.9	11.1	14.5	0.9	10.4	10.7	17.0
B40	13.8	10.2	8.1	7.9	7.8	12.2	0.9	6.4	5.5	9.1
B-	11.8	22.3	17.6	15.0	14.3	NR	15.8	17.6	NT	1.4
Cw1	4.1	NT	1.8[+]	NT	NT	2.0	5.2	NT	NT	1.1
Cw2	2.3	NT	3.0[+]	NT	NT	2.0	2.6	NT	NT	0.7
Cw3	6.4	NT	12.5[+]	NT	NT	8.4	26.4	NT	NT	7.9
Cw4	14.3	NT	22.5[+]	NT	NT	8.9	6.1	NT	NT	14.9
Cw5	3.1	NT	0.6[+]	NT	NT	0.2	NT	NT	NT	3.3
Cw6	17.5*	NT	13.2[+]	NT	NT	1.8	NT	NT	NT	2.2
Cw-	NR	NT	31.2+	NT	NT	NR	59.8	NT	NT	69.9
DR1	4.1	NT	NT	NT	NT	7.3[@]	NT	NT	NT	4.5
DR2	27.7	NT	NT	NT	NT	27.2[@]	NT	NT	NT	19.2
DR3	9.3	NT	NT	NT	NT	14.0[@]	NT	NT	NT	6.8
DR4	9.8	NT	NT	NT	NT	14.0[@]	NT	NT	NT	8.7

Table III - *(cont.)*

HLA allele	Native South Indian (Tamil Nadu) Dravidian Hindus	Native South Indian Tamil Hindus	Native South Indians (Madurai)	South Indian Tamil Hindus (S. Africa)	South Indian Dravidian Hindus (S. Africa)	Native North Indian Aryan Hindus	Native North Indian Hindus I.ucknow)	North Indian Aryan Hindus (S. Africa)	North Indian Aryan Hindus (S. Africa)	South & North Indian Hindus (USA)
	N= 113	N = 240	N = 385	N = 288	N = 424	N = 400	N = 59	N = 193	N = 208	N= 138
	(a)	(b)	(c)	(d)	(e)	(f)	(g)	(d)	(e)	(h)
DR5	12.8	NT	NT	NT	NT	12.3[@]	NT	NT	NT	7.5
DR11	2.2	NT	NT	NT	NT	NT	NT	NT	NT	NT
DR6	8.3*	NT	NT	NT	NT	9.4[@]	NT	NT	NT	2.9
DR7	20.7	NT	NT	NT	NT	11.9[@]	NT	NT	NT	20.6
DR8	5.7*	NT	NT	NT	NT	0.4[@]	NT	NT	NT	4.8
DR9	2.0*	NT	NT	NT	NT	1.5[@]	NT	NT	NT	1.8
DR10	7.4*	NT	NT	NT	NT	1.l[@]	NT	NT	NT	1.8
DR-	0.2	NT	NT	NT	NT	NT	NT	NT	NT	13.1
DR52	51.1	NT	NT	NT	NT	NT	NT.	NT	NT	NT
DR53	25.3	NT	NT	NT	NT	NT	NT	NT	NT	NT
DR-	54.9	NT	NT	NT	NT	NT	NT	NT	NT	NT
DQ1	51.1	NT	NT	NT	NT	NT	NT	NT	NT	NT
DQ2	24.0	NT	NT	NT	NT	NT	NT	NT	NT	NT
DQ3	29.0	NT	NT	NT	NT	NT	NT	NT	NT	NT
DQ-	17.5	NT	NT	NT	NT	NT	NT	NT	NT	NT

a - Present study; b - Selvakumar *et al* [1988]; c - Pitchappan *et al* [1984]; d- Hammond *et al* [1982]; e - Hammond and Asmal [1980]; f- Mehra *et al* [1968]; g - Papiha *et al* [1989]; h - Mittal *et al* [1982];

* - 50; [+] - 85; [@] - 134; NR - Not reported; NT - Not tested.

Table IV - Haplotype frequency (HF), linkage disequilibrium (A) and t-values of HLA haplotypes in South Indian (Tamil Nadu) Hindus of Dravidian descent ($x10^4$) [N = 113).

Haplotype	HF	Chi-square	A	t-value'
A1 - B17	927	12.1	569	3.6
A l - B40	13	4.5	-288	-1.9
A2 - B5	799	3.9	369	2.2
A2 - B51	575	4.2	311	2.2
A10 - B62	127	6.4	112	1.6
A26 - B8	85	4.9	78	1.3
A24 - B51	122	6.4	88	2.0
B35 - Cw4	155	0.1	56	0.6
A1 - DR2	113	6.4	-494	-2.2
A1 - DR3	227	0.1	75	0.6
A1 - DR7	977	8.1	524	3.1
A3 - DR11	127	4.5	108	1.6
B5 - DR4	84	0.0	21	0.3
B8 - DR3	121	2.5	96	1.4
B12 - DR7	366	5.0	243	2.2
B44 - DR7	227	1.7	136	1.5
B13 - DR2	486	4.3	282	2.3
B17 - DR7	1059	21.3	720	4.5
B44 - DR4	200	4.0	151	1.7
B22 - DR6	123	3.9	104	1.5
DR2 - DQ1	2683	25.4	1265	8.4
DR2 - DQ2	35	9.9	-700	-2.8
DR3 - DQ1	140	4.6	-334	-1.6
DR3 - DQ2	690	12.2	466	3.5
DR4 - DQ1	80	6.5	-419	-1.9
DR4 - DQ2	10	4.1	-249	-1.8
DR4 - DQ3	977	27.7	718	5.3
DR5 - DQ3	1031	19.9	693	4.7
DR7 - DQ1	7	14.9	-1052	-3.1
DR7 - DQ2	1528	33.3	1027	6.4
DR7 - DQ3	130	5.1	-420	-2.0
DR11 - DQ3	224	4.1	164	2.3

[+]t - values greater than 2 indicate significant positive linkage disequilibrium and those less than -2 indicate significant negative disequilibrium.

The haplotype frequencies and the linkage disequilibria figures in the Dravidian Hindus of Tamil Nadu are presented in Table IV. Significant positive linkage disequilibrium is noted for haplotypes A1, B17; A2, B5; A2, B51; A1, DR7; B12, DR7; B13, DR2; B17, DR7; DR2, DQ1; DR3, DQ2; DR4, DQ3; DR5, DQ3; DR7, DQ2; DR11, DQ3. Haplotypes A1, DR2; DR2, DQ2 and DR7, DQ1 show negative linkage disequilibrium.

While attempting a comparison, it is interesting to note that though several Indian Hindu groups have been typed for both HLA-A and HLA-B loci, data for HLA-C [Mittal *et al* 1982; Pitchappan *et al* 1984; Mehra *et al* 1986; Papiha *et al* 1989] and HLA-DR loci [Mittal *et al* 1982; Mehra *et al* 1986] are scanty. For DQ locus, the present report appears to be the first for a Hindu sample. From this backdrop of information [Papiha and Mastana 1990], haplotype analysis and comparison reveals A1, B17 to be the most characteristic feature of Indian Hindus (Aryan/Dravidian) [Hammond *et al* 1979; Mittal *et al* 1982; Pitchappan *et al* 1984; Mehra *et al* 1986; Selvakumar *et al* 1988; present study, Table IV]. Haplotypes B12, DR7 and B17, DR7 are also very common [Mittal *et al* 1982; Mehra *et al* 1986; present study, Table IV]. Other haplotypes with significant positive or negative linkage disequilibria presently observed among the native Dravidian Hindus of Tamil Nadu are new to the literature.

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