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Susceptibility of major groups of Tamil Nadu to diseases: 1. Psoriasis vulgaris

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Abstract. Eighty-three patients with psoriasis vulgaris, living in Madurai, Tamil Nadu, India, were studied for HLA–A, HLA–B, HLA–C, HLA–DR and HLA–DQ antigen frequencies and compared with seventy-seven controls studied using the same batch of reagents. A highly significant increase of frequency of HLA–Bw57, a split of HLA–B17, was found in the patients; Bw58, another split of B17, was absent. Relative risk was high for A1, B17, Bw57 and DR7 individuals; it was highest for Bw57. Frequencies of the haplotypes *A1–Bw57* and *DR7–DQw3* were also significantly higher in patients. Analysis of the HLA data based on ethnic differences identified as major groups revealed high relative risk for B17, Bw57 and DR7 only in major group III, a Western brachycephal Armenoid group, but not in major group II, a Mediterranean one thought to be an earlier settler of this region. Analysis of the data based on age and sex subgroups yielded interesting information. The age at onset of the disease in the total patient sample showed a bimodal distribution. The two sexes differed in their age-at-onset distributions: females showed a preponderance of early onset of the disease (< 30 years of age, 68%), while the majority of males had late onset (> 30 years of age, 71%). HLA data for the early-onset patients indicate very high relative risk for B17, Bw57 and DR7. This suggests that psoriasis may be influenced by sex, and that the early-onset and late-onset forms of the disease may be of different aetiopathogenesis. These observations stress the importance of considering the ethnic origin or composition of samples, and age, sex and other parameters in HLA and disease association studies.

Keywords. HLA and disease; psoriasis vulgaris; relative risk.

1. Introduction

The enthusiasm of many workers in the field of HLA is doused by inconsistent results in their HLA and disease association studies. One of the reasons for this is ethnic variation in disease susceptibility (see Tiwari and Terasaki 1985). A disease with known HLA association may show association with different HLA alleles in different ethnic groups (Tiwari and Terasaki 1985). Disease association *may* mean linkage disequilibrium between 'disease-producing' genes or genes that govern immunological processes in the pathogenesis of the disease and an HLA allele or haplotype. Variation in HLA association in different ethnic groups may, in the event of such linkage, be due to crossover events between these 'disease genes' and different HLA alleles in different founder populations. Alternatively, parallel evolution of the 'disease-producing' genes in different populations may result in association with different HLA alleles.

India is known for heterogeneity of people, habits and habitats. It has been suggested that people of Indian descent in Trinidad are at greater risk of cardiac death, and this has been attributed to their genetic make-up (Beckles *et al.* 1986). Our studies on the HLA profile of the people of Tamil Nadu (Pitchappan *et al.*

1984; Rajasekar *et al.* 1987; Kakkaniah *et al.* 1988; Pitchappan 1988) and that of Sanghvi *et al.* (1981) on other genetic and anthropological polymorphisms outlined the ethnic affinities of various populations of Tamil Nadu. Should we select an appropriate disease and parameter we may identify their differential susceptibility to the disease. Towards this goal we selected a skin disorder, psoriasis vulgaris, and studied its HLA association in the major groups of Tamil Nadu. We were prompted to do this by the following facts:

(i) The frequencies of HLA–B17 and haplotype *A1–B17* are relatively high in Indian populations compared to many other races of the world; both the splits of B17, viz. Bw57 and Bw58, are present in India.
(ii) Although many major groups living in Tamil Nadu have been adjudged as Caucasoid based on anthropological and other genetic polymorphisms (Sanghvi *et al.* 1981), the North-European Caucasian *A1–B8* haplotype is absent in all the Indian populations studied so far.
(iii) Some of the population groups of South India, e.g. major group III, possess Caucasian haplotypes like *A3–B7*, *A1–B17* and *A2–B40*, whereas many Oriental haplotypes like *Aw33–Bw44* and *A1–B37* are present in the Indian population in general and in Tamil Nadu in particular (Pitchappan *et al.* 1984; Pitchappan 1988).
(iv) The disease psoriasis vulgaris is associated mostly with HLA–B17 in Caucasian populations but with HLA–B13 in Oriental populations (see Tiwari and Terasaki 1985; Sasazuki *et al.* 1986).

Hence it would be interesting to know whether the established associations of HLA–B13, HLA–B17, HLA–Cw6 and/or HLA–DR7 with psoriasis vulgaris (see Tiwari and Terasaki 1985) exist in the major groups of Tamil Nadu. The results have revealed an association of HLA–Bw57 (a split of B17) with psoriasis vulgaris, and further, a high relative risk for Bw57 only in major group III, which resembles the Western brachycephal Armenoid racial type.

2. Materials and methods

2.1 *Study materials*

A total number of 83 patients with psoriasis vulgaris (plaque type), attending the out-patient ward of the Department of Dermatology, Government Rajaji Hospital, Madurai, for varying periods of time, were studied. The patients were interviewed and clinically assessed by two of us (A.K. and V.R.) in the out-patient skin clinic. Only patients with typical clinical picture of psoriasis vulgaris were included in the study. Of the 83 patients 15 had lesions on the scalp, 14 on the legs, 3 on the arms, 13 had joint involvements in addition to multiple-site lesions, and the rest had different combinations of the various sites affected. Among these 61% responded to treatment, 17% were not responding and had a progressive disease, and the rest, 22%, were on treatment. The nutritional status was poor in 27% of the patients, 58% had an average nutritional status, and the rest were healthier. Fifty-five per cent of the patients had their domicile and work-place in urban areas, 35% in rural areas, and 10% lived in semi-urban areas. It is unfortunate that family histories could not be obtained; this is essentially because of the high incidence of illiteracy among the patients.

A total number of 77 healthy volunteers and staff of our university formed the control group. Their HLA antigen frequencies compare well with the figures given in our previous publication (Pitchappan *et al.* 1984). The proportions of the major groups among them are similar to those in the patient sample (major group II, 29% in controls and 25% in patients; major group III, 26% and 39%; and the rest belonging to other major groups, caste groups and religious groups). The mean age of the control group was $33{\cdot}0 \pm 0{\cdot}8$ and that of the patient group $37{\cdot}0 \pm 1{\cdot}46$. The mean age at onset of disease of the patient group was $31{\cdot}2 \pm 1{\cdot}5$.

2.2 *HLA typing*

The patients were HLA-phenotyped using the III Asia Oceania Histocompatibility Workshop tray (AOH, $n = 52$) and our local research tray (R17). Controls were also HLA-typed at the same time using the AOH trays. Control frequencies compared well with our earlier results (Pitchappan *et al.* 1984). The reliability of phenotyping in these trays was adjudged by serum-versus-antigen, serum-versus-serum and serograph analyses (tables 1 and 2) (Rajasekar 1985; Kakkaniah 1987). Thus the assignment of Bw57 was possible in the AOH tray: this tray contained eight Bw57 + Bw58 sera that gave serum-versus-antigen r values in the range 0·80–0·96 in our hands, four Bw62 + Bw57 sera with r value 0·80–0·92, and four Bw62 sera with r value 0·82–0·92 (tables 1 and 2). Assignments of difficult antigens using duo-specific sera (like Bw57 + Bw58) were essentially made based on serograph analysis. This revealed that Bw58 is not present in the psoriasis patient group. To assign HLA–DR7 antigen five sera were used, three with r value 0·83–0·96 and two with r value 0·72.

For HLA phenotyping the two-stage microlymphocytotoxicity test (Terasaki and McClelland 1964) was employed. Twenty millilitres of venous blood were drawn from each patient or volunteer. A miniature nylon wool column was used to isolate the T and B lymphocytes (Manickasundari *et al.* 1984). Complement for DR and DQ antigen typing was absorbed with buffy coat pooled from ten volunteers before use to remove nonspecific toxicity.

2.3 *Analysis of data*

Data processing was carried out using an Apple IIe computer system. All computer programmes used in this study were developed locally in Apple Pascal language and tested extensively earlier in this laboratory (Pitchappan *et al.* 1984; Rajasekar 1985; Kakkaniah 1987). Gene frequencies (Bernstein formula), their standard errors, haplotype frequencies (Mattiuz formula) and coefficients of linkage disequilibrium were calculated following the methods described in Cavalli-Sforza and Bodmer (1971) and Mather (1967). The t values were calculated as described in Mittal (1976). Relative risk and preventive and aetiologic fractions were calculated as described in Svejgaard *et al.* (1983).

3. Results

3.1 *Comparison of HLA data for controls and patients*

HLA gene frequencies and their standard errors for the controls and the

Table 1. Serograph analysis of HLA-B17 sera in psoriasis patients and controls documenting the presence of HLA-Bw57 in psoriasis patients.

Controls			Patients		
2260 2136 2118 2261 2074 2142 2115	2005 2013 2036 2093 2049 2096 2249 2106	2134 2039 2092 2121 2137 2205 2248	2069 2212 2235	2202 2246	2015 2025 2047 2053 2057 2070 2072 2151 2152 2155 2186 2187 2193 2208 2209 2252 2275 2303 2309 2319 2371 2430
8 8 8 8 1 8 8	1 1 1 1 1 1 1 1	1 1 1 1 1 1 1	8 8 8	1 2	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
4 8 8 8 8 2 8 8	1 1 1 1 1 1 1 1	1 2 1 1 1 1 1	8 8 8	1 1	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 0
8 8 8 8 1 8 8	1 1 1 1 1 1 1 1	1 1 1 1 1 1 1	8 8 8	1 1	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
8 8 8 8 8 8 8	1 1 1 1 1 1 1 1	1 1 1 1 1 1 1	8 8 8	2 8	1 1 1 1 1 1 1 2 1 1 1 8 1 6 1 6 1 1 1 1 1 1
8 8 8 8 6 8 8	1 1 1 1 1 1 4 1	1 4 6 2 1 1 1	8 8 8	6 8	1 6 2 2 1 1 1 4 4 2 6 8 8 1 2 8 2 1 6 6 6 6
1 8 8 8 1 8 8	1 1 1 1 1 1 1 2	1 1 4 2 1 2 1	2 8 8	1 1	1 8 1 2 2 1 1 1 1 1 2 1 1 1 1 1 1 0 0 0 0 0
8 8 8 8 8 8 8	2 1 6 6 1 1 1 8	8 8 8 8 8 8 8	8 8 8	8 8	8 8 8 8 8 8 6 8 8 6 8 8 8 6 6 8 8 8 8 8 8 8
8 8 8 8 8 8 8	1 1 4 1 2 1 1 6	4 2 8 4 4 6 8	8 8 8	4 8	4 8 8 8 8 4 6 4 6 2 8 1 6 6 4 8 1 6 1 6 6 2
8 8 8 8 8 8 8	4 1 4 6 2 1 1 8	8 8 8 8 8 6 8	8 8 8	6 8	8 8 8 8 8 8 2 8 8 8 8 8 8 4 1 8 8 6 8 8 8 8
8 8 8 8 8 8 8	2 1 2 1 4 1 2 4	4 8 1 8 6 2 1	8 8 8	6 8	4 8 6 8 8 8 2 6 4 8 6 8 6 6 1 8 4 8 1 8 8 2
8 8 8 8 6 8 8	8 1 8 8 1 8 8 8	8 8 8 8 8 8 8	8 8 8	8 8	8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8
1 1 1 1 1 1 8	8 8 8 8 8 8 8 8	8 8 8 8 8 8 8	1 1 1	1 1	8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8
1 0 1 1 0 0 0	8 8 8 0 0 8 8 0	8 8 8 6 0 8 1	1 1 1	1 1	0 0 8 8 8 8 0 0 8 8 8 8 8 8 2 8 8 8 0 6 4 1
1 1 1 1 2 1 1	8 8 4 8 8 8 1 8	8 8 8 6 8 8 2	1 1 1	1 1	8 8 8 8 8 8 8 8 8 8 8 8 8 8 2 8 6 8 8 6 8 8
8 2 1 1 1 1 8	8 8 8 8 8 8 8 8	8 8 8 8 8 8 8	8 2 2	1 1	8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8
1 1 2 1 2 1 8	8 8 8 8 8 1 8 8	8 8 8 8 8 8 8	1 1 1	1 1	8 0 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 6 8 8
1 2 1 1 1 1 1	8 1 8 6 8 6 8 4	4 8 8 6 8 1 1	1 6 1	1 1	8 8 8 8 8 8 1 6 8 6 8 8 8 8 6 8 4 8 1 8 8 0
1 2 1 1 1 1 8	8 8 8 8 8 1 1 4	8 8 6 8 8 2 1	1 1 1	1 1	8 8 1 8 8 8 8 6 8 6 8 8 6 8 6 8 8 8 0 0 8 0
2 2 1 1 1 1 2	8 4 8 6 3 1 6 2	4 8 6 4 6 2 1	1 1 1	1 1	8 6 2 8 8 6 4 4 8 6 1 2 2 1 2 8 2 6 1 4 2 0
1 8 0 1 1 1 8	8 0 0 0 8 6 2 4	0 8 1 0 8 8 6	1 1 1	1 2	8 8 0 0 0 8 8 0 1 8 8 8 8 8 8 8 8 8 1 8 6
Antigens:					
a a a a a a a Bw62		c c c c c c c Bw57	a a a Bw62		c c c c c c c c c c c c c c c c c c c c c c c c c Bw57
	b b b b b b b b Bw58			d d Bw63*	

Each individual was tested against a panel of sera. The numbers under each individual are cytotoxicity scores on the NIH reading scale (NIH Pub. No. 80–545): 0 = not readable, invalid; 1 = 0–19% cytotoxicity, negative; 2 = 20–29%, weak negative; 4 = 30–49%, weak positive; 6 = 50–79%, positive; 8 = 80–100%, strong positive.

Serum-versus-antigen *r* value is the correlation in cytotoxicity reactions between a given serum and its antigen in a panel of antigens.

Serum (AOHW id. no.)	Specificities and serum-vs-antigen *r* values	
	III AOHW	In our hands
349	Bw62 0·85	Bw62 0·92
297	Bw62 0·85	Bw62 0·91
350	Bw62 0·83	Bw62 0·84
817	Bw62 0·84	Bw62 0·82
348	B15 0·80	Bw62 0·77
347	Bw62 0·75	Bw62 0·69
816	Bw62 + B46 + B15 0·80	Bw57 + Bw62 0·92*
275	Bw62 + B46 + B15 0·83	Bw57 + Bw62 0·88
274	Bw62 + B46 + B15 0·79	Bw57 + Bw62 0·80
353	Bw62 + B15 + Bw57 0·77	Bw62 + Bw57 0·64
177	Bw62 + B17 + B5 + B15 + B21 0·67	Bw57 + Bw62 + Bw58 + B21 0·81
333	B17 0·93	Bw57 + Bw58 0·96
196	B17 0·92	Bw57 + Bw58 0·88
189	B17 0·87	Bw57 + Bw58 0·88
828	B17 0·78	Bw57 + Bw58 0·86
184	B17 0·91	Bw57 + Bw58 0·85
332	B17 0·83	Bw57 + Bw58 0·84
185	B17 0·84	Bw57 + Bw58 0·84
183	B17 0·81	Bw57 + Bw58 0·80
116	B17 0·62	Bw57 + Bw58 0·73

Such analysis helps in identification of new antigens and splits, and in checking the reliability of their identification. For example: while all patients in the above panel have scored positive against Bw57 + Bw62 (+ Bw63) sera, five patients have scored negative against Bw57 + Bw58 sera; thus the patients who scored positive against both sets of sera are all Bw57; no patient is Bw58.

*Serum-vs-antigen *r* value for Bw63 sera not worked out as only two individuals scored positive.

Table 2. Serum-versus-serum coefficient of correlation values (× 100) for the sera used to assign HLA–Bw57 and HLA–Bw58.

Serum no.																			Serum no.	AOHW id. no.	AOHW key sera*	Specificity and Serum vs. antigen *r* value
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20			
	100	92	75	71	75	55	57	39	48	51	−2	−10	−12	6	−3	−11	2	−11	15	1	349	a	Bw62 0·92
		92	75	71	75	55	57	39	48	51	−2	−10	−12	6	−3	−11	2	−11	15	2	297	a	Bw62 0·91
			69	65	69	49	51	43	52	56	−4	−12	−13	3	−5	−12	0	−12	25	3	350	a	Bw62 0·84
				62	55	46	57	36	38	42	0	−14	−16	−3	−10	−15	−4	−14	3	4	817	a	Bw62 0·82
	Bw 62				65	60	53	47	51	47	16	24	3	20	14	15	15	16	14	5	348	a	Bw62 0·77
						49	51	34	42	35	6	22	−1	3	5	0	12	1	11	6	347	a	Bw62 0·69
							89	71	87	58	56	49	52	55	53	47	56	42	48	7	816	ab	Bw57 + Bw62 0·92
								62	77	54	43	41	38	44	41	32	41	26	38	8	275	ab	Bw62 + Bw57 0·88
									70	52	54	49	47	61	43	51	43	40	48	9	177		Bw57 + Bw62 (+ Bw58 + B21) 0·81
										54	53	46	51	52	50	47	55	43	58	10	274	ab	Bw57 + Bw62 0·80
					Bw62 + Bw57						24	12	24	37	34	27	35	21	39	11	353	ab	Bw62 + Bw57 0·64
												84	85	86	82	81	81	77	69	12	333	bc	Bw57 + Bw58 0·96
													89	72	78	83	77	83	48	13	196	bc	Bw58 + Bw57 0·88
														77	74	86	86	81	66	14	189	bc	Bw57 + Bw58 0·88
										Bw57 + Bw58					73	73	73	69	67	15	828		Bw57 + Bw58 0·86
																70	78	74	59	16	184	bc	Bw57 + Bw58 0·85
																	81	85	54	17	332		Bw57 + Bw58 0·84
																		85	60	18	185		Bw57 + Bw58 0·84
																			39	19	183		Bw58 + Bw57 0·80
																				20	116		Bw57 + Bw58 0·73

The reactions of each serum in the panel are compared with the reactions of every other serum. A coefficient of correlation of 1 between two sera means that they are exactly similar to each other. For example, in the above panel, sera nos. 1 and 2 have a correlation coefficient of 1, such analysis helps in identification of unknown sera by comparison with known or reference sera.

*III AOHW key sera: a, Bw62; b, Bw57; c, Bw58.

psoriasis vulgaris patients are presented in table 3. The antigen distribution chi-square values, relative risk (predisposition to the disease) associated with each antigen, and the aetiologic fractions are also shown. HLA antigens A1, B17, Bw57, Cw2 and DR7 showed relative risk greater than 2·0. The aetiologic fraction was also high for these antigens. The corrected (Yates) chi-square values for disease

Table 3. Comparison of HLA antigen and gene frequencies of psoriasis patients and controls.

HLA antigen	Controls*			Patients†			Chi-square (Yates)	Relative risk	Aetiologic fraction	Preventive fraction
	PF (%)	GF (%)	SEGF	PF (%)	GF (%)	SEGF				
		($n=77$)			($n=83$)					
A1	35·1	19·4	3·4	54·2	32·3	4·0	5·17[b]	2·17	0·29	
A2	24·7	13·2	2·8	34·9	19·3	3·2	1·55	1·62	0·13	
A3	10·4	5·3	1·8	12·1	6·2	1·9	0·01	1·07	0·02	
A9	28·6	15·5	3·0	24·1	12·9	2·7	0·68	0·80		0·06
A10	9·1	4·7	1·7	7·2	3·7	1·5	0·52	0·79		0·02
A11	27·3	14·7	3·0	16·9	8·8	2·3	3·18	0·55		0·12
Aw19	26·0	14·0	2·9	16·9	8·8	2·3	2·56	0·59		0·14
A24**	28·6	15·5	3·0	24·1	12·9	3·3	0·58	0·80		0·06
A26**	9·1	4·7	1·7	5·6	2·8	1·6	1·18	0·64		0·03
A28	13·0	6·7	2·0	4·8	2·4	1·6	2·88	0·44		0·08
A30**	1·3	0·7	0·7	5·6	2·8	1·6	0·77	3·50	0·04	
A31**	9·1	4·7	1·7	3·7	1·9	1·3	2·41	0·45		0·04
A32**	1·3	0·7	0·7	0·0			3·46	0·47		0·00
Aw33**	14·3	7·4	2·2	7·4	3·8	1·9	2·34	0·52		0·07
Aw36**	1·3	0·7	0·7	0·0			3·47	0·47		0·00
Aw68**	9·1	4·7	1·7	1·8	0·9	0·9	4·30	0·26		0·04
Aw69**	3·9	2·0	1·1	3·7	1·9	1·3	0·27	1·01		0·00
A−		5·8			5·5		0·19	1·24	0·06	
B5	24·7	13·2	2·8	30·1	16·4	3·0	0·35	1·31	0·07	
B7	18·2	9·6	2·4	7·2	3·7	1·5	5·44[b]	0·38	0·11	
B8	3·9	2·0	1·1	2·4	1·2	0·9	0·99	0·65		0·01
B12	14·3	7·4	2·2	8·4	4·3	1·6	2·01	0·57		0·06
B13	5·2	2·6	1·3	7·2	3·7	1·5	0·04	1·37	0·02	
B14	0·0			0·0			0·0		0·0	
B15	10·4	5·3	1·8	7·2	3·7	1·8	0·97	0·69		0·03
B16	5·2	2·6	1·3	4·8	2·4	1·2	0·22	0·93	0·00	
B17	18·2	9·6	2·4	53·0	31·5	4·0	19·49[f]	4·93	0·42	
B21	6·5	3·3	1·5	2·4	1·2	0·9	2·72	0·40		0·03
Bw22	5·2	2·6	1·3	6·0	3·1	1·3	0·01	1·14	0·01	
B27	2·6	1·3	0·9	1·2	0·6	0·6	1·52	0·55	0·01	
B35	22·1	11·7	2·7	16·9	8·8	2·3	1·07	0·72	0·06	
B37	19·5	10·3	2·5	6·0	3·1	1·3	7·90[d]	0·28		0·12
B39**	5·2	2·6	1·3	1·8	0·9	0·9	2·10	0·46		0·02
B40	18·2	9·6	2·4	24·1	12·9	2·7	0·52	1·41	0·07	
B44	14·3	7·4	2·2	7·4	3·8	1·9	2·24	0·52		0·07
B49**	5·2	2·6	1·3	1·8	0·9	0·9	2·10	0·46		0·02
Bw50**	1·3	0·7	0·7	0·0			3·46	0·47		0·00
B51**	11·7	6·0	2·0	18·5	9·7	2·9	0·71	1·70	0·08	
Bw52**	13·0	6·7	2·1	14·8	7·7	2·6	0·00	1·18	0·02	
Bw53**	3·9	2·0	1·1	0·0			4·30	0·19		0·00
Bw55**	1·3	0·7	0·6	3·7	1·9	1·3	0·10	2·43	0·02	
Bw56**	3·9	2·0	1·1	0·0			4·30	0·19		0·00
Bw57**	9·1	4·7	1·7	51·9	32·0	5·0	29·50[f]	10·88	0·49	

(*continued*)

Table 3. (*continued*)

HLA antigen	Controls*			Patients†			Chi-square (Yates)	Relative risk	Aetiologic fraction	Preventive fraction
	PF (%)	GF (%)	SEGF	PF (%)	GF (%)	SEGF				
		($n=77$)			($n=83$)					
Bw58**	7·8	4·0	1·6	1·8	0·0		6·37	0·10		0·03
Bw60**	0·0			7·4	3·8	1·9	3·65	13·81	0·07	
Bw61**	18·2	9·5	2·4	9·3	4·7	2·0	2·82	0·49		0·09
Bw62**	10·4	5·3	1·8	7·4	3·8	1·9	0·80	0·73		0·03
B−		8·9			5·9		0·04	1·05	0·01	
		($n=77$)			($n=54$)*					
Cw1	6·5	3·3	1·5	9·3	4·7	2·1	0·06	1·47	0·03	
Cw2	1·3	0·6	0·6	22·2	11·8	2·1	13·29[e]	15·00	0·21	
Cw3	7·8	4·0	1·6	9·3	4·7	2·0	0·00	1·22	0·02	
Cw4	24·7	13·2	2·8	14·8	7·7	2·6	2·54	0·55	0·11	
Cw5	6·5	3·3	1·5	0·0			5·68[b]	0·12		0·00
Cw6	19·5	10·3	2·5	16·7	8·7	2·8	0·41	0·84		0·03
Cw7	28·6	15·5	3·1	20·4	10·8	3·1	1·61	0·65		0·10
C−		49·8			51·5		−0·02	0·72	0·30	
		($n=67$)			($n=52$)*					
DR1	6·0	3·0	1·5	9·6	4·9	2·2	0·16	1·63	0·04	
DR2	44·8	25·7	4·1	34·6	19·1	4·1	1·71	0·66		0·15
DR3	10·5	5·3	2·0	13·5	7·0	2·5	0·05	1·33	0·03	
DR4	20·9	11·0	2·8	25·0	13·3	3·5	0·10	1·26	0·05	
DR5	22·4	11·9	2·9	13·5	7·0	2·5	2·20	0·56		0·10
DRw6	20·9	11·0	2·8	15·4	8·0	2·7	1·01	0·71		0·06
DR7	28·4	15·4	3·3	48·1	27·9	4·8	4·08[a]	2·31	0·27	
DRw8	11·9	6·1	2·1	13·5	7·0	2·5	0·00	1·15	0·02	
DRw9	7·5	3·8	1·7	7·7	3·9	1·9	0·09	1·05	0·00	
DRw10	13·4	7·0	2·2	11·5	5·9	2·3	0·35	0·86	0·02	
DRw11	9·0	4·6	1·8	3·8	1·9	1·4	2·17	0·47		0·04
DRw12	13·4	7·0	2·2	7·7	3·9	1·9	1·67	0·57		0·06
DR−	0·0			0·0			1·67	0·57	0·06	
DQw1	78·6	53·7	5·3	65·4	41·2	5·6	3·34	0·52		0·38
DQw2	7·1	3·6	1·6	28·8	15·6	3·7	8·73[d]	4·92	0·23	
DQw3	54·3	32·4	4·4	59·6	36·5	5·4	2·90	0·58	0·25	
DQ−		10·3			6·7		2·90	0·58	0·26	

PF, Phenotype (antigen) frequency; GF, gene frequency; SEGF, standard error of gene frequency.
Chi-square (with Yates' correction) is for association between antigen and disease. Significance: [a]$P<0·05$, [b]$P<0·025$, [c]$P<0·01$, [d]$P<0·005$, [e]$P<0·001$, [f]$P<0·0001$.

$$\text{Relative risk} = \frac{\text{no. of ag-positive patients} \times \text{no. of ag-negative controls}}{\text{no. of ag-negative patients} \times \text{no. of ag-positive controls}}.$$

Aetiologic fraction (when $RR>1$) $=[(RR-1)/RR]hp$;
Preventive fraction (when $RR<1$) $=(1-RR\times hp)/[RR(1-hp)+hp]$;
where RR is relative risk and hp is the frequency of antigen-positive patients.

*Typed using AOH tray; **54 individuals typed using AOH tray.

†Of the 83 individuals, 54 typed using AOH tray and 29 using R17 tray; antigen frequency estimates from the two trays comparable, hence data pooled.

association were highly significant ($P<0.0001$) for B17 and Bw57. Although Cw2 showed a very high relative risk and chi-square value there were problems with assignment of this antigen using III AOH sera (Pitchappan and Omori 1986) and also with assignment of DQw2 and hence they will not be discussed further. B13 and Cw6 did not show any increased risk of the disease in this population (table 3). When we divided the patients into subgroups, frequency of B40 was higher in the subgroup of patients with progressive disease (those who did not respond to treatment, 7/15; B40 in patients responding to treatment, 6/53). When we analysed

Table 4. List of selected haplotypes with significant positive linkage disequilibrium (shown as delta value $\times 10^4$) in various subgroups of psoriasis patients and controls.

	Haplotype	Frequency (per 10,000)	Chi-square	$\Delta \times 10^4$	t value
Controls ($n=77$)					
	A1–B17	632	6·4[b]	435	2·5
	A1–Bw57	343	2·9	240	1·8
	B17–DR7	645	9·0[d]	475	2·7
	Bw57–DR7	529	14·0[e]	440	2·9
	B8–DR3	223	21·2[f]	213	1·8
	DR7–DQw3	446	0·0	65	0·3
	DR7–DQw2	330	12·3[e]	287	2·4
	DR2–DQw1	2187	17·4[f]	1169	7·1
	DRw53–DR7	1686	14·4[f]	1002	5·7
	DR4–DQw3	863	10·9[e]	588	3·7
Patients (unclassified, $n=54$)					
	A1–B17	1982	10·1[d]	1085	4·0
		*2436	27·2[f]	1393	6·9
	A1–Bw57	1982	10·1[d]	1085	4·0
	B17–DR7	1878	10·4[d]	1063	4·0
	Bw57–DR7	1878	10·4[d]	1063	4·0
	B8–DR3	191	6·9[e]	178	1·5
	DR7–DQw3	2231	15·6[e]	1303	5·3
	DR7–DQw2	1244	11·5[e]	843	3·7
	DR2–DQw1	1835	13·9[e]	1117	5·5
	DRw53–DR7	1479	0·3	538	
Patients, age at onset < 30 years ($n=24$)					
	A1–B17†	**2875	10·1[d]	1521	5·2
	B17–DR7	3040	3·3	1257	2·8
	Bw57–DR7	3040	2·3	1257	2·8
	DR7–DQw3	3693	8·5[d]	1854	5·4
	A1–B17	2012	4·2[a]	1096	9·1
	A1–Bw57	2012	4·2[a]	1096	9·1
Patients, age at onset > 30 years ($n=29$)					
	A1–B17	***2047	15·3[e]	1284	5·1
	A1–B17	2036	6·2[b]	1186	3·4
	A1–Bw57	2036	6·2[b]	1186	3·4
	B17–DR7	1054	4·3[a]	722	2·5
	Bw57–DR7	1054	4·3[a]	722	2·5
	DR7–DQw3	1290	6·3[b]	896	3·2
	DR4–DQw3	1290	6·3[b]	896	3·2
	DR2–DQw1	2344	8·3[d]	1376	4·9

Table 4. (*continued*)

	Haplotype	Frequency (per 10,000)	Chi-square	$\Delta \times 10^4$	*t* value
Female patients ($n=21$)					
	A1–B17	1956	3·0	1162	3·2
	A1–Bw57	1956	3·0	1162	3·2
	B17–DR7	1676	4·9[a]	1048	2·9
	Bw57–DR7	1676	4·9[a]	1048	2·9
	DR7–DQw3	2338	6·1[b]	1434	3·7
	DR2–DQw1	2441	5·5[b]	1409	4·3
Male patients ($n=33$)					
	A1–B17	2598	24·3[f]	1559	7·1
	B17–DR7	901	4·9[a]	537	2·6
	Bw57–DR7	960	19·1[f]	762	3·4
	DR7–DQw3	2131	7·5[c]	1220	3·8
Major group III patients ($n=25$)					
	A1–B17	2679	3·6	1233	3·2
	A1–Bw57	2679	3·6	1233	3·2
	B17–DR7	2974	4·7[a]	1389	3·7
	Bw57–DR7	2974	4·7[a]	1389	3·7
	DR7–DQw2	2000	4·2[a]	1327	8·4
	DR7–DQw3†	3024	5·0[b]	1677	8·8

Haplotype frequency calculated by Mattiuz formula (Mattiuz *et al.* 1970).
Chi-square is for association between genes in haplotype.
[a,b,c,d,e,f] Significance: *P* as in table 3.
*$n=83$, **$n=34$, ***$n=48$. †Absent in matched controls.

the patients with joint involvement we could not find any difference in antigen frequency from the rest of the patients. Hence we pooled the data and made further analyses. There was no difference in the antigen frequencies when the data were analysed based on the site of lesions.

Haplotype analysis (table 4) revealed very high frequencies of haplotypes *A1–B17*, and *A1–Bw57*, *B17–DR7* and *Bw57–DR7* in patients compared to those in controls. The *t*-values were also higher for these haplotypes in the patient sample. Chi-square for haplotype *DR7–DQw3* was significant only in the patients. Further, this haplotype was present in significantly high frequency in major group III patients and in all subgroups of patients. Frequency of haplotype *A1–B17* was significantly higher in male patients.

3.2 *Age at onset*

The mean age at onset for the entire group of patients (total, $n=83$) was $31{\cdot}2 \pm 1{\cdot}5$ (figure 1). However, when the sexes were analysed separately, the males showed a mean age at onset of $35{\cdot}0 \pm 1{\cdot}4$ and the females $24{\cdot}0 \pm 1{\cdot}5$. S.D. Mean age at onset for males and females differed significantly ($P<0{\cdot}001$), suggesting an early onset of the disease in females. Five-year age class histograms (figures 2 and 3) show this clearly. The histograms for the entire group of patients (total), and male and female patients (figure 2) reveal that while 29% of male patients had onset before the age of 30, 68% of female patients had early onset (24% and 71% respectively in AOH tray, figure 3). In the total sample 41% of the patients had early onset. The age class

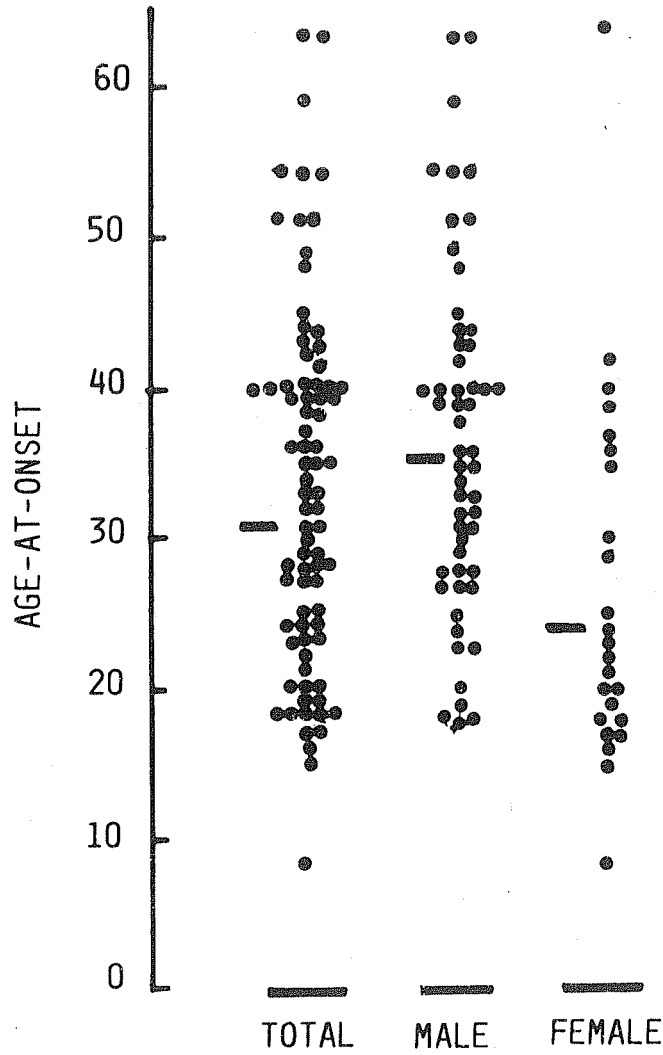

Figure 1. Age at onset of psoriasis vulgaris for the total patient sample ($n=83$), male patients ($n=58$) and female patients ($n=25$).

histograms for the total sample show a bimodal distribution, the first peak corresponding to the mean age at onset of the female patients.

Table 5 presents relative risks for selected HLA antigens for early-onset and late-onset patients and for major group II and major group III patients. It is essential to mention here that there was no significant difference in any of the antigen frequencies between the <30-years and >30-years control groups. When the early-age-at-onset and late-age-at-onset patients were compared with appropriate age-matched controls, the early-onset group showed high relative risk for B17, Bw57 and DR7 (11·6, 18·0 and 4·8 respectively) and high values of aetiologic fraction (0·56 to 0·62). In the late-onset group only Bw57 showed a significant relative risk of 7·4. Thus the early-onset form of the disease may be 'controlled' by HLA–Bw57 and HLA–DR7, but the late-onset form only by Bw57. This was reflected in haplotype

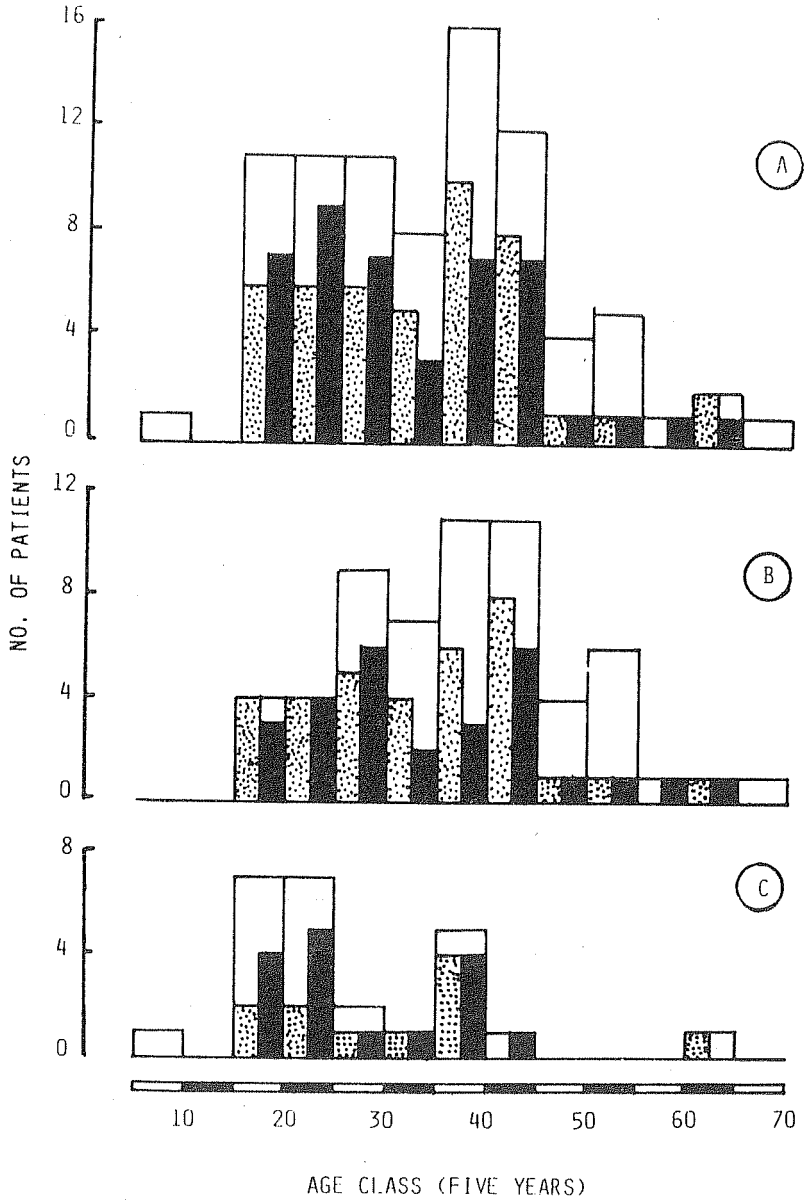

Figure 2. Five-year age-at-onset-class histograms for (A) total patient sample ($n = 83$), (B) male patients ($n = 58$) and (C) female patients ($n = 25$). Each age class includes a dotted bar for number of patients with HLA–A1 antigen and a solid bar for number of patients with HLA–B17.

analysis as well: the early-onset group ($n = 24$) had a frequency (per 10,000) of the *DR7–DQw3* haplotype of 3693 (P of $\chi^2 < 0{\cdot}005$, table 4).

3.3 *Differences between the sexes*

The age class histograms (figures 2 and 3) also show the numbers of patients

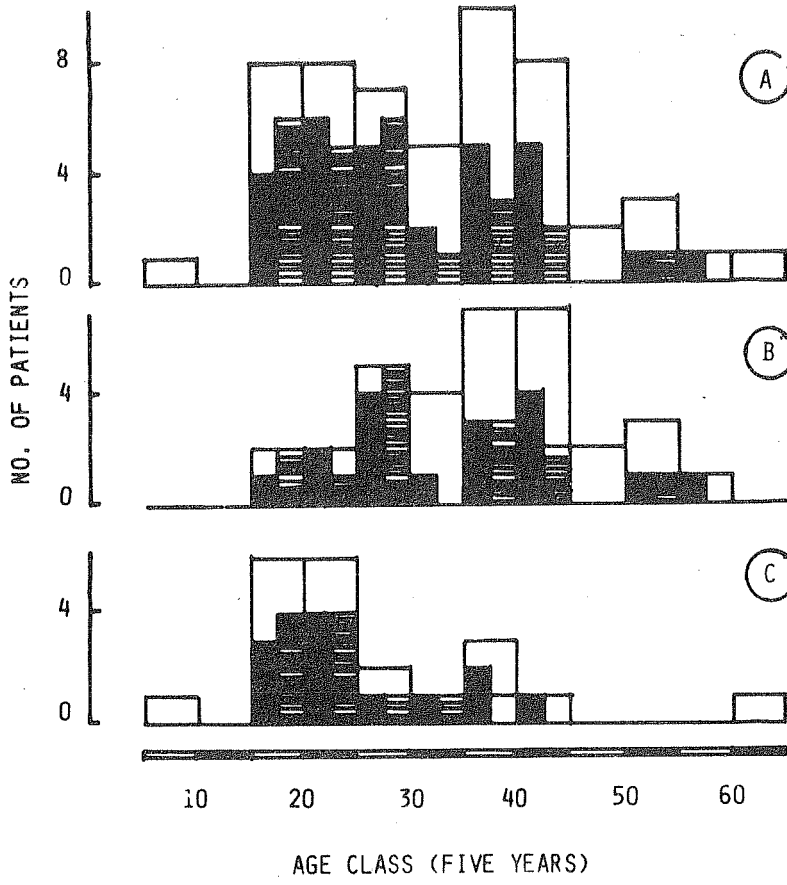

Figure 3. Five-year age-at-onset-class histograms for (A) unclassified patients ($n = 54$), (B) male patients ($n = 33$) and (C) female patients ($n = 21$) typed using AOH tray. Solid bars show number of Bw57-positive patients and hatched bars show number of DR7-positive patients.

possessing various HLA antigens shown to confer high relative risk of psoriasis, viz. A1, B17, Bw57 and DR7 (table 3). Again one can observe a difference between the sexes: most of the early-onset males possess A1, B17, Bw57 and DR7; most of the early-onset females also possess B17, Bw57 and DR7, but the number of early-onset female patients with A1 is low. This prompted us to analyse the antigen and haplotype frequencies in patients and the correlation with the disease. The early-onset patients, female patients and patients belonging to major group III had a high proportion of patients with Bw57 and DR7 (72 and 52%). Hence Bw57 may predispose to psoriasis, and the effect of DR7 may be additive, resulting in early onset (also see above, § 3·2). The data suggest that in the probable extended haplotype or supratype associated with disease A1–Bw57–DR7–DQw3, Bw57 may predispose to the disease in the first place, and DR7 and DQw3 may be involved in causing early onset.

Table 5. Selected HLA antigen frequencies in various subgroups of psoriasis patients and controls.

Subgroup	Patients, n_1/total	Controls, n_2/total	Chi-square (Yates)	Relative risk	Aetiologic fraction
HLA–A1					
< 30 yrs	18/34 (53%)	10/29 (34%)	1·5	2·1	0·28
> 30 yrs	26/48 (54%)	13/44 (30%)	4·7[a]	2·7	0·35
M. G. II	13/21 (62%)	12/29 (41%)	1·3	2·2	0·34
M. G. III	17/31 (55%)	9/25 (36%)	1·3	2·1	0·29
Total	45/83 (54%)	27/77 (35%)	5·2[b]	2·2	0·29
HLA–B17					
< 30 yrs	23/34 (70%)	4/29 (14%)	16·4[f]	11·6	0·62
> 30 yrs	20/48 (42%)	9/44 (20%)	3·6	2·7	0·26
M. G. II	9/21 (43%)	6/29 (21%)	1·9	2·8	0·27
M. G. III	21/31 (68%)	5/25 (20%)	10·6[d]	7·6	0·59
Total	44/83 (53%)	14/77 (18%)	19·5[f]	4·9	0·42
HLA–Bw57					
< 30 yrs	15/24 (63%)	2/29 (7%)	16·2[e]	18·0	0·59
> 30 yrs	13/29 (45%)	4/44 (9%)	10·6[d]	7·4	0·39
M. G. II	3/11 (27%)	4/29 (14%)	0·3	2·3	0·16
M. G. III	18/25 (72%)	2/25 (8%)	8·8[d]	23·2	0·69
Total	29/54 (54%)	7/77 (9%)	29·5[f]	10·9	0·48
HLA–DR7					
< 30 yrs	17/24 (71%)	8/25 (32%)	5·9[b]	4·8	0·56
> 30 yrs	7/27 (26%)	9/38 (24%)	0·0	1·1	0·03
M. G. III	14/24 (52%)	10/23 (43%)	0·5	1·2	0·23
Total	25/52 (48%)	19/67 (28%)	4·1[a]	2·3	0·27

[a,b,c,d,e,f]Chi-square significance as in table 3. Only 11 individuals were typed for HLA–DR7 in major group II; data not shown.

3.4 *Psoriasis in major groups of Tamil Nadu*

We have shown earlier that the various major groups and caste groups of Tamil Nadu differ significantly from one another in their HLA antigen and haplotype frequencies (Pitchappan *et al.* 1984; Rajasekar *et al.* 1987). In the patient sample studied here, there were 21 patients belonging to major group II and 30 patients belonging to major group III. Frequencies of HLA–B17 and HLA–Bw57 (a split of B17) were remarkably high in major group III. Relative risk was highest (23·2, table 6) for Bw57 in major group III. This result stresses the importance of considering the ethnic origin and composition of the sample in data processing and interpretation, even when the different ethnic groups live in the same region.

The results were also analysed based on the involvement of joints and the distribution of lesions but no significant differences were observed between the various subgroups. There was no clear distinction between B17-positive and B17-negative patients with reference to age at onset, as observed by Svejgaard *et al.* (1974): ethnic differences may be responsible for this discrepancy.

Table 6. Selected HLA haplotype and gene frequencies and relative risk of psoriasis for selected HLA genes in various populations of Tamil Nadu.

	Population						
	Tot	I	II	Kal	III	IV	Iyer
Haplotype frequencies (per 10,000)							
A1–B17	565[c]	645[a]	310	340	535[d]	335	860[d]
A3–B7	205[d]	0	374[b]	140	200[b]	177	270
A2–B40	286[c]	951	95	0	420[a]	67	80
A19–B12	157[c]	163	96	0	54	620[b]	960[c]
A10–B8	72[b]	0	189[c]	712[c]	0	0	0
Gene frequencies (%)							
A1	13	12	14	15	12	18	17
B17	10	9	10	10	12	9	10
Bw57	5		7		4		
Relative risks							
A1	2·1		2·2		2·1		
B17	4·9		2·8		7·6		
Bw57	10·9		2·3		23·2		

Tot, Total sample ($n=575$), Kal, Kallars; Iyer, Iyers; I, II, III and IV are major groups of Tamil Nadu (Pitchappan *et al.* 1984; Rajasekar *et al.* 1987).
[a]$P<0·05$, [b]$P<0·01$, [c]$P<0·001$, [d]$P<0·0001$, [e]$P<0·00001$.

4. Discussion

The present study on psoriasis vulgaris has extended the established Caucasian association of HLA–B17 with this disease (Russel *et al.* 1972; White *et al.* 1972; Tiwari and Terasaki 1985) to a South Indian population. The bimodal age-at-onset histograms and the preponderance of early age at onset in females presented here compare well with the results of Svejgaard *et al.* (1974) and Gunawardena *et al.* (1978) respectively. The analysis of the data based on age at onset, sex and major groups yielded interesting information. Relative risk and haplotype frequency together strongly suggest involvement of DR7, Bw57 and DQw3 in early-age-at-onset, female and major group III patients. It was suggested during the III AOH Workshop multicentric study that some alleles of the complement component C4 may be involved in the disease process (Sasazuki *et al.* 1986). Of 19 psoriasis patients of our sample tested for C4 polymorphism at this workshop, 6 had A1, B57, DR7 and DQw3 antigens and all of them had C4A.6. It is probable that these HLA specificities and complement alleles may be involved in the immunopathogenesis of the disease. In a recently proposed mechanism (Valdimarsson *et al.* 1986), the process leading to psoriatic lesions is triggered by T lymphocytes within the epidermal compartment.

The results further extend the observation that psoriasis in this population is associated with HLA–Bw57, a split of HLA–B17, but not with Bw58, another split of B17 (tables 1 and 2). The association seems to be similar to that in Caucasians rather than the one in Japanese, where an association with HLA–B13 was reported

(see Sasazuki *et al.* 1986). The association of psoriasis with B13 and B17 in an American Caucasian population was first described by Russel *et al.* (1972) and White *et al.* (1972). Since then several investigators have observed these associations in Caucasian patients from the United States, Canada and various European and Asian countries. An effort was made during the Seventh International Histocompatibility Workshop and the III AOH Workshop to study patients from different ethnic groups (Hawkins *et al.* 1980; Sasazuki *et al.* 1986). These studies have reported an association with HLA–B13 in Oriental populations and with B17 in Caucasoid populations and Ashkenazi Jews (Batchelor and Morris 1977; Gazit *et al.* 1978; Tsuji *et al.* 1979; Hawkins *et al.* 1980; Tilikainen *et al.* 1980; Chan *et al.* 1981; Marcusson *et al.* 1981).

Association of HLA–DR7 with psoriasis in a group of 40 French patients was reported by Raffoux *et al.* (1980). This association has been subsequently confirmed by several workers in Caucasians (Hawkins *et al.* 1980; Marcusson *et al.* 1981; Tiwari *et al.* 1982) and in Japanese (Tsuji *et al.* 1979; Hawkins *et al.* 1980). The present study has also revealed an association of this disease with DR7, but essentially with early-onset cases. This is contradictory to the report of Tiwari *et al.* (1982), where, although they found an association with DR7, they could not find a difference between the different age-at-onset groups.

The presence of the classical Caucasian association of HLA–B17 (Bw57) with psoriasis in a Caucasian population of Tamil Nadu, viz. major group III, suggests that this disease (gene?) must have been inherited by them as a result of a founder effect. It is interesting to note the absence of similar association in major group II, an earlier settler in this region. It is evident from table 6 that the allele frequencies of *A1*, *B17* and *Bw57* are about the same in the different major groups and caste groups; nonetheless psoriasis is associated with B17 and Bw57 only in major group III. This may mean hitchhiking of the disease (gene?) along with Bw57 in major group III but not in the other groups. It may be quite premature, however, to come to this conclusion on the basis of the results from the small sample of the present study. An in-depth study of this issue, involving DNA restriction-fragment-length polymorphisms in the *HLA* locus, the more recently identified *DQ* alleles (Bodmer 1988), and a larger sample size, is warranted.

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