HLA-Cw6 and the Genetic Predisposition to Psoriasis: a Meta-Analysis of Published Serologic Studies

To the Editor:

Postulated genetic factors in psoriasis include human leukocyte antigen associations. HLA-Cw6 is the most frequently described association and has been confirmed in many racial groups. The frequency of many HLA-C alleles, however, is underestimated by serology and some antigens such as HLA-Cw6 are thought to be consistently assigned incorrectly by serology (Bunce *et al*, 1996). The low surface expression of HLA-C molecules together with the lack of typing reagents account for the fact that 20%–50% of populations studied so far carry undefined HLA-C alleles, collectively called Cw "blank" (Levine and Yang, 1994). Using a high resolution polymerase chain reaction with sequence-specific primers we have recently reported the strong association of HLA-Cw*0602 in a U.K. Caucasian population with chronic plaque psoriasis (Mallon *et al*, 1997), HIV-associated psoriasis (Mallon *et al*, 1998), and streptococcal associated guttate psoriasis.[1]

Case-control HLA association studies are limited by the fact that control populations may be derived from a different gene pool. Recent evidence from genetic linkage studies supports a role for the HLA-C locus in the pathogenesis of chronic plaque psoriasis; linkage to the major histocompatibility complex region on chromosome 6p21 (including to the HLA-C locus) has been demonstrated indicating that one or more genes located within the major histocompatibility complex and close to class I HLA loci may represent the major determinant of the genetic basis of psoriasis (Trembath *et al*, 1997). We thought it worthwhile to examine all available published data on the association of HLA-Cw6 with psoriasis. We have examined data from serologic studies investigating HLA-C antigens in psoriasis and included all studies that provided usable data up to December 1998. The results emphasize the importance of HLA-C, or a gene in linkage disequilibrium with HLA-C, in the predisposition to psoriasis, particularly in guttate psoriasis and psoriasis of early onset.

Medline, PubMed, and EMBASE database searches were performed to obtain all published serologic studies available from 1966 to December 1998: MeSH (medical subjects heading) terms used were "immunogenetics and psoriasis"; "HLA and psoriasis"; and "HLA-C and psoriasis". References were also sought from published research by using the Science Citation Index and by searching references in published studies and abstracts. The search was not restricted to the English language. Inclusion criteria for studies incorporated in the meta-analysis were that: (i) HLA-Cw6 was included in the investigation of HLA associations in patients with psoriasis; (ii) a control population without psoriasis was also studied; and (iii) a study did not use the same data as previous studies. The search uncovered 14 studies (Brenner *et al*, 1978; Murray *et al*, 1980; Tiilikainen *et al*, 1980; Laurentaci *et al*, 1982; Armstrong *et al*, 1983; Economidou *et al*, 1985; Ozawa *et al*, 1988; Nakagawa *et al*, 1991; Chablani *et al*, 1992; Cao *et al*, 1993; Ikäheimo *et al*, 1994; Roitberg-Tambur *et al*, 1994; Gonzaga *et al*, 1996; Schmitt-Egenolf *et al*, 1996) that met these inclusion criteria. Relevant data (HLA-C phenotype frequencies in cases and controls) were extracted from the published papers obtained (**Table I**). Odds ratios, confidence limits, and significance values for HLA-Cw6 were calculated (**Table II**) using Epi Info Version 6 (1996). Meta-analysis was performed on the results of HLA-Cw6 typing by logistic regression using the Stata Statistical Package (Stata Statistical Software, 1997). Baseline odds for psoriasis in Cw6 negative patients was estimated for each individual study and a common odds ratio, interpreted as the relative risk, was estimated over all studies. Robust variance formulae were used to calculate confidence limits, allowing for the possibility that true relative risks might vary slightly from one study to another, so that the common relative risk would be an appropriately weighted average. Meta-analysis was performed on studies in each of five psoriasis subgroups: group 1, early-onset psoriasis; group 2, late-onset psoriasis; group 3, guttate psoriasis (one study only); group 4, psoriasis of unspecified type; group 5, psoriasis vulgaris. Three studies (Brenner *et al*, 1978; Tiilikainen *et al*, 1980; Schmitt-Egenolf *et al*, 1996) were included in the meta-analysis of more than one group.

Meta-analysis (**Table III**) showed that HLA-Cw6 predicted guttate psoriasis more strongly than type I psoriasis, and type I psoriasis more strongly than type II psoriasis. The other two types of psoriasis (vulgaris and unspecified) are probably mixtures of these three types and show intermediate odds ratios.

This meta-analysis is of limited value because publication bias makes it more likely that significant positive associations are published compared with non-significant associations (Easterbrook *et al*, 1991) and an accurate meta-analysis should include unpublished data (Bland, 1995). In order to include unpublished data in the meta-analysis of HLA-Cw6 serologic typing results in psoriasis, we invite the contribution of unpublished HLA-C serologic typing results to the authors of this letter.

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[1]Mallon E, Bunce M, Savoie H, Gotch F, Bunker CB: HLA-Cw*0602 and guttate psoriasis. *J Invest Dermatol* 110:618, 1998 (abstr.)

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Table I. HLA-Cw6 typing results in serologic studies used in meta-analysis

Psoriasis type	Study (country)	Cases Cw6 +ve	Controls Cw6 +ve	Cases Cw6 –ve	Controls Cw6 –ve
I[a]	Brenner *et al*, 1978 (Austria)	48	32	9	93
I[b]	Schmitt-Egenolf *et al*, 1996 (Germany)	49	31	11	115
II[c]	Brenner *et al*, 1978 (Austria)	9	32	11	93
II[d]	Schmitt-Egenolf *et al*, 1996 (Germany)	13	31	17	115
Guttate	Tiilikainen *et al*, 1980 (Finland)	16	34	6	428
Unspecified	Brenner *et al*, 1978 (Austria)	57	32	20	93
Unspecified	Murray *et al*, 1980 (USA)	30	17	30	109
Unspecified	Armstrong *et al*, 1983 (England)	42	32	12	121
Unspecified	Economidou *et al*, 1985 (Greece)	33	30	58	172
Unspecified	Ozawa *et al*, 1988 (Japan)	27	13	77	937
Psoriasis vulgaris	Tiilikainen *et al*, 1980 (Finland)	17	34	20	428
Psoriasis vulgaris	Laurentaci *et al*, 1982 (Italy)	54	24	68	152
Psoriasis vulgaris	Nakagawa *et al*, 1991 (Japan)	7	0	72	100
Psoriasis vulgaris	Chablani *et al*, 1992 (India)	36	37	31	95
Psoriasis vulgaris	Cao *et al*, 1993 (China)	2	1	10	99
Psoriasis vulgaris	Ikäheimo *et al*, 1994 (Finland)	35	10	30	178
Psoriasis vulgaris	Roitberg-Tambur *et al*, 1994 (Israel)	7	46	21	212
Psoriasis vulgaris	Gonzaga *et al*, 1996 (Brazil)	13	20	9	139
Psoriasis vulgaris	Schmitt-Egenolf *et al* 1996 (Germany)	62	31	28	115

[a]Age of onset between 10 and 20 y.
[b]Age of onset $<$ 30 y.
[c]Age of onset between 35 and 45 y.
[d]Age of onset $>$ 40 y.

Table II. Odds ratio for HLA-Cw6 and psoriasis from serologic studies

Psoriasis type	Study	n	Odds ratio	95% CL[a]	p-value[b]
I[c]	Brenner *et al*, 1978	57	15.50	6.50, 39.39	0.000000
I[d]	Schmitt-Egenolf *et al*, 1996	60	16.62	7.30, 38.94	0.000000
II[e]	Brenner *et al*, 1978	20	2.38	0.79, 6.94	0.106200
II[f]	Schmitt-Egenolf *et al*, 1996	30	2.84	1.13, 6.95	0.018900
Guttate	Tiilikainen *et al*, 1980	22	33.57	11.37, 109.83	0.000000
Unspecified	Brenner *et al*, 1978	77	8.28	4.14, 16.75	0.000000
Unspecified	Murray *et al*, 1980	60	6.41	2.95, 14.07	0.000000
Unspecified	Armstrong *et al*, 1983	54	13.23	5.93, 30.54	0.000000
Unspecified	Economidou *et al*, 1985	91	3.26	1.75, 6.05	0.000094
Unspecified	Ozawa *et al*, 1988	104	25.27	11.95, 55.25	0.000000
Psoriasis vulgaris	Tiilikainen *et al*, 1980	37	10.70	4.75, 23.63	0.000000
Psoriasis vulgaris	Laurentaci *et al*, 1982	122	5.03	2.78, 9.20	0.000000
Psoriasis vulgaris	Nakagawa *et al*, 1991	79	∞	1.92, ∞	0.002794
Psoriasis vulgaris	Chablani *et al*, 1992	67	2.98	1.54, 5.75	0.000570
Psoriasis vulgaris	Cao *et al*, 1993	12	19.80	0.90, 1178.95	0.029923
Psoriasis vulgaris	Ikäheimo *et al*, 1994	65	20.77	8.89, 51.31	0.000000
Psoriasis vulgaris	Roitberg-Tambur *et al*, 1994	28	1.54	0.52, 4.03	0.440371
Psoriasis vulgaris	Gonzaga *et al*, 1996	22	10.04	3.40, 29.88	0.000004
Psoriasis vulgaris	Schmitt-Egenolf *et al*, 1996	90	8.21	4.34, 15.61	0.000000

[a]Confidence limits.
[b]Fisher's exact (two-tailed) p value is given.
[c]Psoriasis vulgaris "including eruptive type, plaque type and seborrhoeic type"; age of onset between 10 and 20 y.
[d]"Chronic stable psoriasis"; age of onset $<$ 30 y.
[e]Psoriasis vulgaris "including eruptive type, plaque type and seborrhoeic type"; age of onset between 35 and 45 y.
[f]"Chronic stable psoriasis"; Age of onset $>$ 40 y.

Table III. Meta-analysis of serologic studies

Psoriasis type	No of studies	Odds ratio	p value	95% confidence interval
Type I	2	16.04	0.000	9.17, 28.07
Type II	2	2.63	0.003	1.40, 4.94
Guttate	1	33.57	0.000	12.32, 91.45
Unspecified	5	8.48	0.000	6.21, 11.57
Psoriasis vulgaris	9	6.46	0.000	4.99, 8.36

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