

## LETTER TO JMG

## Streptococcal infection distinguishes different types of psoriasis

P Weisenseel, B Laumbacher, P Besgen, D Ludolph-Hauser, T Herzinger, M Roecken, R Wank, J C Prinz

*J Med Genet* 2002;**39**:767-768

## Key points

- The link between streptococcal tonsillitis and first onset of psoriasis is well known.
- Here we show that streptococcal infection is confined to a particular subtype of non-pustular psoriasis, which is defined by early onset ( $\leq 40$  years), a positive family history, and the HLA molecules Cw6, B13, or B57.
- This suggests distinct inherited immune response patterns to streptococcal antigens as a key to understanding the pathogenesis of psoriasis.

Epidemiologically, the first manifestations of psoriasis are promoted by upper respiratory tract infections with *Streptococcus pyogenes*. Parallels to post-streptococcal disorders are obvious but still lack pathogenetic proof. Two types of non-pustular psoriasis, types I and II, can be distinguished according to age of onset, family history, and inheritance of certain HLA alleles. Here we show that only type I but not type II psoriasis is associated with streptococcal infection.

Psoriasis vulgaris is a chronic inflammatory disease that affects 1.5-2% of people in western societies with severe and disabling inflammation of the skin and, occasionally, arthritis. It is currently regarded as an autoimmune-like disorder that is mediated by antigen specific activation of T cells in the skin of genetically predisposed subjects.<sup>1</sup> A high incidence of streptococcal throat infections as the main trigger of first psoriasis exacerbation<sup>2,3</sup> favours streptococcal antigens as causative agents that may induce cross reactive T cell responses against skin components.<sup>4,5</sup> In this respect, psoriasis behaves like rheumatic fever, which follows upper respiratory tract infections with *Streptococcus pyogenes*.<sup>6</sup>

The streptococcal trigger and genetic background of psoriasis suggest that psoriasis patients may display a particular, genetically determined sensitivity to streptococcal infection.

In order to define this predisposition better, we correlated the incidence of streptococcal infection, HLA class I antigens, family history, and age of onset in patients with chronic plaque psoriasis. Results were compared to the incidence of infection with *Staphylococcus aureus* that may worsen psoriasis.<sup>7</sup>

## METHODS

HLA class I typing was performed serologically for 42 specificities (14 A, 20 B, 8 C) in 96 white patients with non-pustular chronic plaque psoriasis; there were 26 females and 70 males (mean age 48 (SD 16) years, mean duration of psoriasis 15 (SD 13) years, mean age of onset 33 (SD 18) years).

Evidence of microbial infection was assessed by nasopharyngeal swabbing and standard methods of bacteria isolation and determination of anti-streptolysin-O (ASLO) and anti-desoxyribonuclease B (ADNase-B) serum antibody titres (normal range  $< 200$  IU/ml each) resp. anti-staphylolysin titre (ASTA, normal range  $< 2$  IU/ml).

Psoriasis patients were classified according to the following definitions. Type I psoriasis: early onset ( $\leq 40$  years of age) and/or positive family history and/or inheritance of HLA-Cw6, -B57, or -B13. Type II psoriasis: late onset ( $> 40$  years), lack of positive family history, and lack of predisposing HLA antigens.<sup>8,9</sup> Additionally, subtyping was carried out according to age of onset and HLA pattern as suggested by Szczerkowska-Dobosz *et al*<sup>10</sup>: type Ia/IIa, early/late onset psoriasis without the predisposing HLA antigens Cw6, B57, or B13; type Ib/IIb, early/late onset with typical psoriatic HLA antigens. The type IIa patients are identical to the type II patients classified according to Henseler and Christophers,<sup>8</sup> while subgroups Ia, Ib, and IIb correspond to type I patients.

## RESULTS

HLA typing showed a significantly increased frequency of HLA-Cw6, -B57, and -B13 in psoriasis patients compared to 367 healthy controls ( $p < 0.001$  each), confirming earlier

**Table 1** Streptococcal and staphylococcal infection parameters in type I and II psoriasis and four psoriasis subtypes

	Psoriasis type (No of patients/% of total)		Subtypes (No of patients/% of total)				HLA-Cw6/-B57/-B13 (No of patients/% of total)	
	Type I	Type II	Ia	Ib	IIa	IIb	Positive	Negative
Total number of subjects	82	14	31	38	14	13	51	45
<i>Streptococcus pyogenes</i> ASLO-/ADNase-B titre $> 200$ IU and/or nasopharyngeal swabbing positive	32 (39%)	0 (0%)*	9 (29%)†	17 (45%)‡	0 (0%)	6 (46%)§	23 (45%)	9 (20%)¶
<i>Staphylococcus aureus</i> ASTA titre $> 2$ IU and/or nasopharyngeal swabbing positive	33 (40%)	4 (29%)	13 (42%)	15 (39%)	4 (29%)	5 (38%)	20 (39%)	17 (38%)

\* $p=0.004$  type I v type II. † $p=0.04$  type Ia v IIa. ‡ $p=0.002$  type Ib v IIa. § $p=0.006$  type IIb v IIa (two tailed Fisher's exact test each); ¶ $p=0.01$  HLA positive v negative (chi-square test).

findings.<sup>9</sup> Evidence of group A streptococcal infection was found exclusively in type I psoriasis patients (table 1). The difference compared to type II patients was significant ( $p=0.004$ ). A dominant role of HLA antigens over the age of onset in predisposing to streptococcal infection was suggested when psoriasis subtypes were considered. Irrespective of the age of disease onset, psoriasis patients with the typical HLA antigens showed a similar prevalence of streptococcal infection (type Ib 45%, type IIb 46%), whereas signs of streptococcal infection appeared to be slightly less frequent in type Ia patients with early onset but lacking HLA-Cw6, -B57, and -B13 (29%), and they were completely missing in type IIa patients ( $p=0.002$  type Ib v IIa,  $p=0.006$  type IIb v IIa,  $p=0.04$  type Ia v IIa, table 1). In contrast, assessed parameters for *Staphylococcus aureus* (table 1) did not differ significantly between types I and II or type Ia/b and type IIa/b patients.

## DISCUSSION

In distinct ethnic subgroups, susceptibility to rheumatic fever has been shown to depend on the prevalence of particular HLA class I or class II alleles, resulting in a pathological immune response pattern to streptococcal antigens.<sup>6</sup> The HLA class of psoriasis as a disease involving autoreactive T cells but not antibodies is thought to involve mainly HLA class I, with HLA-Cw6, -B57, and -B13 conferring the highest risk.<sup>8</sup> HLA-Cw6 shows strong linkage disequilibrium with -B57 and -B13.<sup>9</sup>

A former study had suggested that HLA-B13 may predispose to severe streptococcal infection.<sup>11</sup> Furthermore, decreased ASLO titres had been observed in HLA-B13 positive psoriasis patients.<sup>12</sup> At the time of these studies, neither HLA-Cw6 nor the psoriasis subtypes had been identified. We failed to detect significant differences in streptococcal infection when comparing patients carrying HLA-Cw6 either alone or together with -B57 and/or -B13.

In a control group of 19 healthy subjects expressing HLA-Cw6, -B57, or -B13, only two subjects showed serological evidence of streptococcal infection. This incidence of streptococcal infection was significantly lower than in type I psoriasis patients ( $p=0.029$ ) or in type Ib ( $p=0.016$ ) and IIb patients ( $p=0.038$ ), while it did not differ significantly from psoriasis patients lacking HLA-Cw6, -B57, or -B13 (type Ia  $p=0.17$ , type IIa  $p=0.49$ ) ( $p$  value determined by two tailed Fisher's exact test). Therefore, we speculate that the predisposition to streptococcal infection in type I psoriasis is preferentially linked with HLA-Cw6 but may involve a genetic trait other than HLA-Cw6 itself. This is supported by the observation that although Cw6 confers the highest risk for psoriasis, only ~10% of Cw6 positive subjects actually develop psoriasis.<sup>13</sup>

Collectively, our findings clearly show that susceptibility to streptococcal infection distinguishes two clinically and genetically defined types of psoriasis. They furthermore indicate that

psoriasis patients expressing HLA-Cw6, -B57, or -B13 show a significantly higher incidence of streptococcal infection parameters, implying distinct inherited immune response patterns to streptococcal antigens as a key to understanding psoriasis pathogenesis. Accordingly, type I psoriasis as the subtype related to streptococcal infection may serve as a model disease to elucidate the mysterious pathomechanisms of post-streptococcal disorders in general.

## ACKNOWLEDGEMENTS

We thank T Henseler for helpful comments. This study was supported by the Deutsche Forschungsgemeinschaft (SFB 571).

## Authors' affiliations

**P Weisenseel, P Besgen, D Ludolph-Hauser, T Herzinger, M Roecken, J C Prinz**, Department of Dermatology, University of Munich, Frauenlobstrasse 9-11, D-80337 Munich, Germany  
**B Laumbacher, R Wank**, Institute for Immunology, University of Munich, Munich, Germany

Correspondence to: Professor J C Prinz, Department of Dermatology, University of Munich, Frauenlobstrasse 9-11, D-80337 Munich, Germany; joerg.prinz@lrz.uni-muenchen.de

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