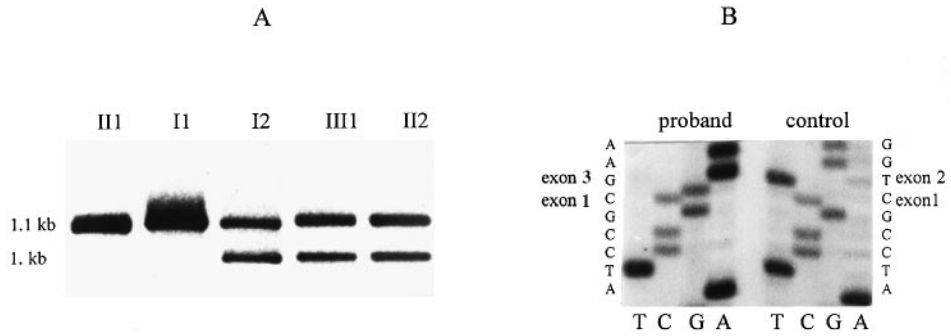

Figure 1. Exon 2 skipping in the human ferrochelatase cDNA. (*A*) Three per cent agarose gel electrophoresis of reverse transcriptase polymerase chain reaction-amplified ferrochelatase mRNA. The proband (II2), his mother (I2), and his daughter (III1) exhibit a normal polymerase chain reaction product (1.1 kb) and a short product, indicating the loss of ≈100 bp of cDNA. (*B*) Ferrochelatase cDNA sequence showing the loss of exon 2 in the patient.

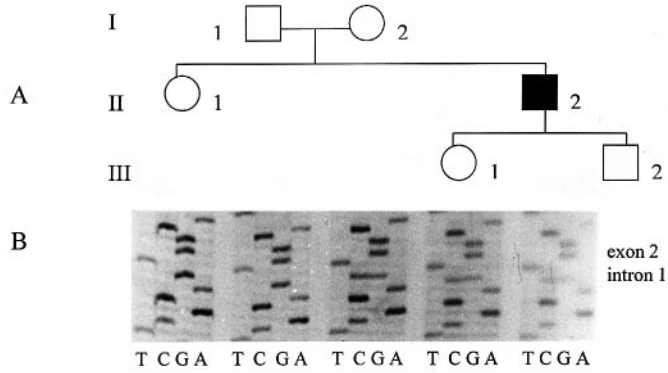

Figure 2. Identification of the mutation among the members of the family. (*A*) Pedigree. Proband with clinical symptoms is indicated by black shading. (*B*) Direct sequencing of intron 1/exon 2 boundary of ferrochelatase gene showing the G→C tranversion at IVS1–1 in the proband II2, his daughter III1, and his mother I2.

genomic DNA were therefore sequenced to determine whether or not a splice mutation was responsible for the loss of exon 2. The results showed that the mutation is indeed a G→C transversion at the acceptor site, IVS1–1, and has not been previously reported. The same mutation, but showing incomplete penetrance, was found in his mother and daughter (**Fig 2**, I2, III1).

An IVS1–23 C→T mutation was also found in the proband, his relatives (I1, II1, and III1) without the IVS1–1 G→C mutation, and two other unrelated erythropoietic protoporphyria patients (data not shown). This mutation was reported previously as a possible cause of exon 2 skipping (Nakahashi *et al*, 1992), but later refuted (Wang *et al*, 1994) when it was found in all erythropoietic protoporphyria patients and in some controls, suggesting that it may play some role in the pathogenesis of erythropoietic protoporphyria.

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Is Human Papillomavirus Type 5 the Putative Autoantigen Involved in Psoriasis?

To the Editor:

While it is well recognized that psoriasis is a T cell-mediated inflammatory disease that results in epidermal proliferation (Griffiths and Voorhees, 1996), the identity of the antigen(s) responsible for T cell activation is still a matter of debate, as recently discussed by Nickoloff and Wrone-Smith (1998). A strong correlation has been found between acute guttate psoriasis and streptococcal infections (Baker *et al*, 1993), and it has been proposed that some bacterial surperantigens or antigens might activate T cells (Telfer *et al*, 1992; Baker *et al*, 1993; Valdimarsson *et al*, 1995; Boehncke, 1996; Norris *et al*, 1997). It was also hypothesized that superantigen-activated T cells might induce abnormal expression of keratin variants that show close homology with streptococcal M protein, and might stimulate M protein-specific autoreactive T cells (Valdimarsson *et al*, 1995). It should be stressed, however, that although T cells specific for M protein have been detected in patients with psoriasis, they have as yet not been shown to cross-react with any skin components.

Based on the model of human skin grafted onto SCID mice, it was recently postulated that there are two steps in the autoimmune pathways to psoriasis (Nickoloff and Wrone-Smith, 1998). The first step is considered to be a polyclonal activation of Vβ restricted $CD4^+$ T cell subsets by some bacterial superantigens (Boehncke *et al*, 1996; Wrone-Smith and Nickoloff, 1996). These activated T cells, injected intradermally into the grafted uninvolved psoriatic skin, induced histologic changes

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resembling psoriasis. It was hypothesized that the second step involves an autoreactive subset of superantigen-preactivated T cells, which recognize a putative autoantigen in the epidermis (Nickoloff and Wrone-Smith, 1998). This assumption found confirmation in the studies by Gilhar *et al* (1997), who showed that psoriatic lesional T cells, but not peripheral blood lymphocytes, were responsible for the maintenance of psoriatic phenotype in the grafted skin. This is also supported by the findings of prolonged expression of CD69 molecules on autologous and superantigen-preactivated T cells administered intradermally into uninvolved psoriatic graft, which presumably are subsequently activated by putative autoantigen (Nickoloff and Wrone-Smith, 1998); however, the autoantigen has not been identified.

Our recent study (Favre *et al*, 1998) strongly suggests that this putative autoantigen could be the L1 capsid protein of HPV5, a virus specific of the rare genetic skin disease epidermodysplasia verruciformis (EV) (Orth, 1987; Majewski and Jablonska, 1995). With the use of a very sensitive nested polymerase chain reaction approach, we demonstrated the presence of HPV5 DNA in scrapings of lesional skin in about 90% of a large series of patients with psoriasis. Most patients were found infected with at least another HPV5-related EV HPV genotype. In contrast, no HPV5 DNA was detected in atopic dermatitis, another T cell-mediated common inflammatory cutaneous disorder. Importantly, with the use of an enzyme-linked immunosorbent assay and HPV5 L1 protein assembled into virus-like particles bearing conformational epitopes, we detected HPV5-specific antibodies in about 25% of 155 patients with psoriasis *versus* only 2%–5% of control individuals, including patients with atopic dermatitis, allograft recipients, and patients with genital warts (Favre *et al*, 1998). Moreover, antibodies to the minor L2 capsid protein of HPV5 were found in an additional 5% of psoriatic patients (Favre, Ait-Ouarabi, and Orth, unpublished data). The almost constant presence of HPV5 and other EV HPV in psoriatic lesions, and the detection of antibodies to conformational epitopes of HPV5 capsid in a proportion of patients, point to a possible role of EV HPV in the immunopathogenesis of psoriasis.

Indeed, papillomavirus infection of keratinocytes is favored by epidermal proliferation and, in turn, established infection leads to proliferation of basal keratinocytes. Multiplication of these nonlytic viruses is restricted to terminally differentiating keratinocytes and viral capsid proteins are detected only in superficial layers of infected epidermis (Orth, 1987). It might thus be hypothesized that nonspecific stimuli, e.g., mechanical injury (Koebner phenomenon) or superantigen-activated T cells, trigger epidermal proliferation that may promote EV HPV5 infection. Because the intraepidermal $CD8^+$ T cells were found to show oligoclonal Vβ expression consistent with classical antigen activation (Chang *et al*, 1997), it could be speculated that this virus is the putative autoantigen.

Psoriasis has an evident genetic component (Schmitt-Egenolf *et al*, 1996; Trembath *et al*, 1997) and this background may overcome the strong host restriction observed in the general population towards HPV5 infection (Orth, 1987). The association of psoriasis with a particular MHC haplotype (Schmitt-Egenolf *et al*, 1996) would possibly allow immune reaction against HPV5 capsid epitopes. It is conceivable that HPV5 antibodies recognize viral capsid epitopes in the stratum corneum, which is a main target of immune reaction in psoriasis (Beutner *et al*, 1987). This might result in complement activation and chemoattraction of polymorphonuclear leukocytes (PMN) into the stratum corneum (Munro abscesses), which is a unique feature of psoriasis. Other chemoattractive stimuli, such as IL-8 and various products of arachidonic acid metabolism released by PMN, may contribute to leukocyte recruitment; however, they also mediate other inflammatory diseases, in which Munro abscesses are absent.

The pathogenic significance of HPV5 and also possibly other related EV HPV in psoriasis requires further study; however, the high prevalence of HPV5 in psoriatic scales and the detection of specific antibodies in a significant proportion of patients strongly suggest that this cell-associated virus might be involved in the autoimmune pathomechanism of psoriasis.

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