

High Prevalence of a Variety of Epidermodysplasia Verruciformis-Associated Human Papillomaviruses in Psoriatic Skin of Patients Treated or not Treated with PUVA

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Epidermodysplasia verruciformis-associated human papillomaviruses and in particular human papillomavirus type 5 were recently shown to be highly prevalent in psoriatic skin. We have analyzed lesional skin from 54 psoriasis patients for infections with genital-specific and epidermodysplasia verruciformis-specific human papillomaviruses to define the spectrum of involved human papillomavirus types and to test if it is influenced by psoralen ultraviolet A therapy. Using polymerase chain reaction analysis we could detect human papillomavirus sequences in skin lesions of 83% of the tested patients. In contrast, human papillomavirus-DNA was only demonstrated in 19% of skin samples from 42 dermatologically healthy, immunocompetent individuals. Sequence analysis of the polymerase chain reaction amplimers revealed 14 human papillomavirus types, all belonging to the epidermodysplasia verruciformis or epidermodysplasia verruciformis-related papillomaviruses. Only in one case we identified sequences related to those of genital viruses, which, however, represented a putatively new human papillomavirus type. The most pre-

valent human papillomavirus type in our patient series was human papillomavirus type 36, found in 62% of the patients positive for human papillomavirus-DNA, followed by human papillomavirus type 5 (38%) and human papillomavirus type 38 (24%). Multiple infections with two to five different human papillomavirus types could be detected in skin samples of 63% of the analyzed patients. The overall human papillomavirus detection rate did not differ significantly between patients which have been subjected to psoralen ultraviolet A photochemotherapy or solely treated with topical preparations (77 vs 89%). Human papillomavirus type 5, however, could be detected significantly more frequent in lesions of psoralen ultraviolet A-treated patients ($p < 0.001$). Our data strongly argue for infections with epidermodysplasia verruciformis-specific papillomaviruses being an almost consistent feature of the lesional psoriatic skin and substantiate the importance of further studies to elucidate a possible involvement of human papillomaviruses in psoriasis pathology. *Key words: epidermodysplasia verruciformis/human papillomavirus/psoriasis/psoralen ultraviolet A. J Invest Dermatol 113:122-126, 1999*

Human papillomaviruses (HPV) are etiologic agents of many epithelial tumors in humans. A broad spectrum of HPV-induced pathologies ranges from common warts to neoplastic lesions of the *cervix uteri* (Shah and Howley, 1996; Gross and Barasso, 1997). Numerous recent studies reported on the presence of HPV sequences in precancerous and malignant skin tumors (for review see Pfister and ter Schegget, 1997). A particularly high prevalence of HPV-DNA could be demonstrated in skin tumors of immunosuppressed transplant recipients. Surprisingly, a substantial proportion of involved HPV types turned out to belong to the large group of HPV types, originally believed to be exclusively associated with tumors of epidermodysplasia verruciformis (EV) patients (Orth, 1987; Fuchs and Pfister, 1996). The EV syndrome is a rare, lifelong

persisting skin disease which depends on some still not characterized defect(s) of the cell-mediated immunity (Orth, 1987; Jablonska and Majewski, 1994). EV patients develop multiple flat warts and macular skin lesions which will frequently give rise to squamous cell carcinomas. The specific cytopathic effects of EV-associated HPV have only sporadically been observed apart from the EV syndrome but seroepidemiologic studies always suggested a widespread occurrence of EV-HPV in the general population (Steger *et al*, 1990; Stark *et al*, 1998). This was substantiated by the demonstration of EV-specific HPV-DNA in many normal skin and plucked hair samples (Astori *et al*, 1998; Boxman *et al*, 1997). Sequencing of polymerase chain reaction (PCR) amplification products from such specimens and from skin tumors of non-EV patients revealed classical EV-specific types but also to a large extent putatively new, EV-related types (Berkhout *et al*, 1995; Shamanin *et al*, 1996; Bens *et al*, 1998). The spectrum of HPV types thus differed from EV patients and particularly HPV5 and HPV8, which are most prevalent in EV, were only rarely detected (Pfister and ter Schegget, 1997).

An extraordinary high prevalence of EV-HPV has recently been reported for skin lesions of psoriasis patients (Favre *et al*, 1998a).

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Abbreviation: EV, epidermodysplasia verruciformis.

Table I. Detection of HPV-DNA in samples of normal and psoriatic skin

Tested specimens	PCR primers (% positives)				
	GP5 ⁺ /6 ⁺	CP 70/65-69/66	HPV5 type specific	HPV36 type specific	Total positive
Skin lesions from (n = 54) psoriatic patients	0 ^a n = 0 ^b	70 n = 38	30 n = 16	52 n = 28	83 n = 45
Skin specimens from (n = 42) healthy donors	0 n = 0	14 n = 6	0 n = 0	10 n = 4	19 n = 8

^aPercent possible samples.^bAbsolute number of positive samples.**Table II. Frequency of detection of individual HPV types in psoriatic lesions**

HPV type	No. of positive cases	% of positive cases
36	28	62
5	16	36
38	11	24
RTRX9	6	13
RTRX1, 19	5	11
23, 24, 25	3	7
8, 9, 15, 20	2	4
RTRX7	1	2
Unknown type (SW1)	1	2

HPV5 turned out to be the most prominent type, followed by HPV36, HPV20, and HPV38. Psoriasis is a noncontagious dermatosis with genetic predisposition, occurring world-wide with morbidity rates of 1.5–2% in caucasians (Christophers, 1996). In most of the cases, the disease persists lifelong with many recurrent episodes, induced by a broad variety of different factors. The pathogenesis of psoriasis is still unclear, although it certainly involves T cell mediated inflammatory reaction(s) which results in promotion of the uncontrolled regenerative epidermal proliferation (Christophers, 1996; Griffiths and Voorhees, 1996). The nature of factor(s) or antigen(s), responsible for priming the involved T lymphocytes is still a matter of controversy (Majewski *et al*, 1998; Nickoloff and Wrone-Smith, 1998). In view of the new virologic data on psoriasis Majewski *et al* (1998) hypothesized that the major capsid protein of HPV5 may play a part as putative autoantigen active in immunopathology of psoriasis.

A widely used and generally highly effective anti-proliferative treatment in psoriasis consists of topical or systemic administration of psoralen, followed by irradiation with UVA light (PUVA). Both these agents can potentially influence interactions between keratinocytes and the infecting HPV. In order to evaluate this relationship and to characterize the spectrum of the involved HPV types we studied a collective of 54 psoriasis patients treated or not treated with PUVA for the presence of HPV-DNAs in their lesional skin.

MATERIALS AND METHODS

Patients and biopsy material Biopsy material from lesional skin of 54 psoriasis patients was obtained to verify the diagnosis. The majority of studied patients (n = 48) originated from Tirol, Austria, the remaining six cases were from Poland. The patients were immunocompetent individuals with a mean age of 48.5 y (range 17–74) and presented with typical skin lesions of chronic stationary plaque (n = 44), acute eruptive guttate (n = 3), pustular (n = 2), or arthropathic (n = 3) psoriasis. The medication consisted of topical steroids, dithranol preparations, and retinoids, combined or not with PUVA. In the latter regimen doses of 10–500 J per cm² were applied in most of the cases (22 patients). Only four patients were treated with high cumulative PUVA doses. Therapy with > 2000 J per cm² was initiated in these cases more than 20 y ago, before emergence of squamous cell carcinoma of the skin was first reported as an adverse effect in PUVA patients in 1979 (Morison *et al*, 1998). All specimens were taken from active lesions at the beginning of a new disease/therapy episode. The control group consisted of 42 healthy, immunocompetent individuals

undergoing nevus excisions (mean age 43.0 y, range 16–79). All specimens showed a normal epidermis on histologic examination with nevus cells in the basal layer, junctional zone, or deeper dermis. No changes suggestive of HPV infection were present in the excised skin clinically or histologically. Patients neither suffered from diseases associated with immunosuppression or immunosuppressive therapy nor were therapeutic UV irradiations reported in the patients' history.

DNA extraction Total cellular DNA was extracted from biopsies using the QIAmp Tissue Kit (Qiagen, Hilden, Germany) according to manufacturer's protocol. The quality of each DNA preparation was controlled by a PCR test for the cellular β -globin gene (Saiki *et al*, 1985) and only positive cases have been included in further analyses.

Detection of HPV sequences DNA preparations were examined for the presence of HPV sequences by PCR analysis with primers, chosen to detect a broad spectrum of HPV types. The two primer sets used were: GP5⁺/GP6⁺ (De Roda Husman *et al*, 1995), specific for HPV types typically infecting the genital mucosa and CP65/CP70 + CP66/CP69, designed by Berkhout *et al* (1995) as a nested PCR approach for the detection of EV-associated papillomaviruses. The presence of HPV5-DNA and HPV36-DNA in biopsy material was re-evaluated in all cases by means of a type-specific PCR test according to Favre *et al* (1998a). The DNA amplification was performed with 100–400 ng template and AmpliTaq Polymerase (Perkin-Elmer, Langen, Germany) in the Mastercycler 5330 (Eppendorf, Hamburg, Germany) according to protocols, published for all the primer pairs used. To avoid contamination of samples during DNA preparation and the PCR processing, the suggestions of Kwok (1990) were strictly observed.

DNA sequencing For sequence analysis PCR amplicons were preparatively separated in 2% agarose gels, the specific bands excised and the DNA was purified using the QIAquick gel extraction kit (Qiagen, Hilden, Germany). The isolated DNA fragments were cloned into the pCR-Blunt vector (Invitrogen, De Schelp, the Netherlands), transformed in *Escherichia coli* TOP10 cells and the recombinant bacterial clones were isolated due to a highly specific anti-suicidal selection. Plasmids from at least 10 colonies each were digested with *Eco*RI to release the cloned inserts. Representative clones showing both the expected and deviating inserts have been subjected to sequence analysis. Sequencing was performed with the Taq FS BigDye-terminator cycle sequencing system using the ABI Prism 377 automatic sequencer (Applied Biosystems, Langen, Germany).

Sequence analysis Sequence analyses were performed using the BLAST 2.0 (Altschul *et al*, 1997) and MacVector 6.5 (Oxford Molecular Group PLC, U.K.) program packages. EMBL, GenBank, DDBJ, and PDB served as sequence databases.

Statistical analysis Differences in DNA prevalences were evaluated by χ^2 and confidence interval (CI) analysis using the SPSS Base System, version 6.1 (SPSS, Chicago, IL).

RESULTS

HPV sequences in clinical samples of psoriatic skin Specimens of psoriatic skin lesions from 54 patients were tested for the presence of HPV sequences by means of PCR analysis. To cover a broad spectrum of HPV types, two sets of PCR primers have been employed which preferentially detect genital-specific and EV-specific papillomavirus types, respectively. The results of the PCR screening are summarized in **Table I**. Using the nested PCR approach with primers CP 70/65–69/66, papillomavirus sequences could be found in 38 of 54 studied

Table III. Distribution of HPV-DNA in skin lesions of PUVA-treated and nontreated patients

	HPV-positive cases	Number of HPV types per person	HPV5-positive cases	HPV36-positive cases	HPV38-positive cases	HPV8-positive cases
Previous PUVA treatment > 2000 J per cm ² (n = 4)	4 (100%)	3.8	3 (75%)	4 (100%)	1 (25%)	2 (50%)
Previous PUVA treatment ≤ 500 J per cm ² (n = 22)	16 (73%)	2.0	10 (46%)	12 (55%)	3 (14%)	0 (0%)
No PUVA treatment (n = 28)	25 (89%)	1.5	3 (11%)	12 (43%)	7 (25%)	0 (0%)

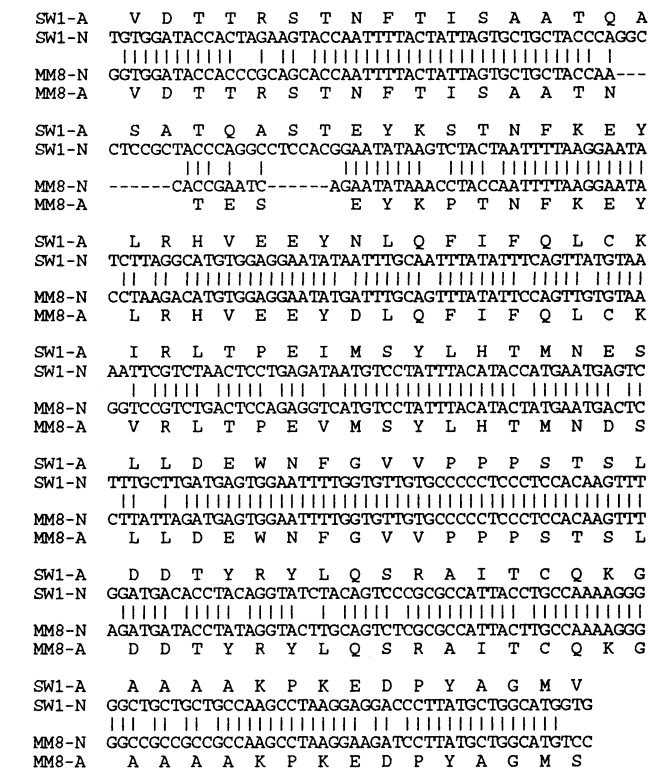


Figure 1. Nucleotide- and protein-sequence alignment of SW1 and MM8 within the PCR-amplified parts of their L1 genes. N: DNA sequence, A: amino acid sequence according to the one letter-code. The accession number of the PCR-amplified sequence of a putatively new HPV type SW1 is AJ012757.

biopsies (70%), indicating a high prevalence of papillomavirus infections in psoriatic skin. No HPV-DNA could be detected in psoriatic lesion using the single-step PCR test with primers GP5⁺/GP6⁺, specific for HPV types infecting the genital mucosa. In view of the reported frequent occurrence of HPV5 and HPV36 in the psoriatic dermis (Favre *et al*, 1998a), all cases were subsequently analyzed by PCR tests with the corresponding type-specific primers. These experiments revealed seven further cases being positive for HPV-DNA, which led to a total HPV prevalence in the studied psoriatic collective of 83%. The majority of tested specimens represented typical psoriatic plaques. Also lesions of guttate (n = 3), pustular (n = 2), and arthropathic (one of three) psoriasis, however, were positive for HPV-DNA.

In contrast, HPV-DNA could be detected only in 19% of random biopsies from 42 dermatologically healthy, immunocompetent subjects.

A variety of HPV types infects skin lesions of psoriasis patients In order to classify HPV types detected in psoriatic skin, all PCR amplimers were cloned and sequenced. As shown in **Table II**, all, except one, identified HPV sequences represented either well-known EV-associated papillomaviruses or related HPV

types of the RTRX-series, characteristic for skin tumors of immunosuppressed renal transplant recipients (Berkhout *et al*, 1995; Bens *et al*, 1998). The most prevalent HPV types in the analyzed collective were HPV36, HPV5, and HPV38, found in lesions of 62, 36, and 24% of the psoriasis patients, respectively. The additional 11 identified HPV types occurred in 2–13% of the analyzed patients. A characteristic feature of the studied biopsies were common multiple infections: in 39 of 54 cases (63%) 2–5 different HPV types could be detected.

Analysis of the PCR-positive nevus excisions used as control samples revealed only the presence of single infections with HPV types 23, 25, and 36. HPV36 was identified in four of eight of these specimens.

A comparison of sequences amplified in this study from a part of the open reading frame L1 with those from available databanks revealed no case of perfect identity. The individual sequences of the most prevalent HPV36 showed, e.g., 97%–99% homology with the reference isolate (Myers *et al*, 1997). These findings are in line with the well-recognized genetic variability of HPV types. In one of the tested psoriasis lesions a putatively new HPV type could be identified (SW1). The 352 bp sequence determined from its L1 gene displayed over 329 bp 86.6% homology to MM8, an HPV isolate from a case of cervical dysplasia (Manos *et al*, 1994; **Fig 1**). In addition, 15 bp absent in the MM8 sequence coded in frame for two inserts of three and two amino acid residues of the L1 protein, respectively. This presumably new virus type should belong to genital mucosa-specific HPV of the phylogenetic group A3 (Myers *et al*, 1997).

HPV infections and photochemotherapy The tested collective consisted of two groups of psoriasis patients roughly equal in number, which have or have not been treated by PUVA photochemotherapy. As PUVA regimen can be expected to influence the course of an HPV infection, we examined the occurrence of HPV-DNA in psoriatic skin lesions of both these patient groups (**Table III**). The overall prevalence of HPV infections did not significantly differ. Infections with multiple HPV types, however, were significantly more frequent in PUVA-treated individuals (80% vs 42% in PUVA nontreated persons; p = 0.01, CI 0.12; 0.64). There is also some indication that the average number of HPV types per patient increases with PUVA treatment and doses (**Table III**). Regarding the distribution of individual HPV types infecting the lesional psoriatic skin, it turned out that in contrast to other identified viruses, HPV5 could be detected almost 5-fold more frequently in samples of the PUVA-medicated individuals (p < 0.001; CI 0.30; 0.70). HPV8, which represents another EV cancer-associated HPV type was detected twice only in the group of patients treated with high doses of PUVA.

DISCUSSION

The results of our PCR screening demonstrated a very high prevalence of HPV sequences in the psoriatic skin. More than 80% of the tested patients scored positive with primers, which allow detection of a broad spectrum of the genital and EV-associated HPV types. The observed prevalence of HPV-DNA in psoriatic lesions was 4.5 times higher than in samples from healthy individuals, which strongly argues for a specific association of HPV infections with psoriatic disease of the skin. The high HPV-DNA detection

rate appears at least generally independent of photochemotherapy because no significant differences could be observed between patients who were and those who were not treated with PUVA. These results are in line with data of Favre *et al* (1998a, b). They could be explained by the increased epidermal proliferation rates in psoriasis, which stimulate replication of the pre-existing HPV-DNA in lesions and thus facilitate their subsequent detection. The activated HPV might also be involved in the autoimmune pathomechanism of psoriasis as had been proposed by Majewski *et al* (1998).

Sequence analysis of the PCR amplimers identified 11 classical EV-associated HPV types (5, 8, 9, 15, 19, 20, 23, 24, 25, 36, 38) and three of their close relatives (RTRX1, 2, 9). A putatively new sequence (SW1) was most closely related to MM8, which belongs to subgroup A3 of the genital/mucosal HPV together with HPV types 61, 62, and 72 (Myers *et al*, 1997). Besides appearing in anogenital intraepithelial neoplasia, HPV61 was sporadically detected in squamous cell carcinoma and Bowen's disease of the skin (Shamanin *et al*, 1996; Mitsuishi *et al*, 1997). More than one HPV type was detected in over 60% of the patients. It has been interesting to note that infections with three to five HPV types preferentially occurred in PUVA-treated patients. This may point to generally increased levels of viral DNA, allowing the detection of HPV that persist besides the dominant type in individual patients.

In contrast to data of Favre *et al* (1998a), the dominating HPV type in our patient series was HPV36 and not HPV5 (63% vs 37%). HPV36 was also the most prevalent virus type in the skin samples of healthy controls. Further, HPV38 could be found relatively frequently (26%). It was originally isolated from a melanoma (Scheuerlen *et al*, 1986), although a recent study failed to confirm its association with melanoma tumors (Astori *et al*, 1998).

It is presently difficult to comment on the different prevalences of individual HPV types reported by Favre *et al* (1998a) and in this study. It should be kept in mind that despite identical PCR protocols for the detection of HPV-DNA, the sensitivity for individual types may be affected by technical differences such as blot hybridization following PCR amplification (Favre *et al*, 1998a). On the other hand it should be noted that both studies also differ with regard to the origin of the analyzed collectives (Polish *versus* mostly Tirolean patients). Last but not least, the patients may differ in their natural life-time sun exposure and/or cumulative doses of UV irradiation in the course of PUVA therapy.

Favre *et al* (1998b) observed no difference in HPV5 DNA positivity among patients who were currently, previously or never under PUVA therapy with doses between 1 and 212 J per cm². We found a 5-fold higher prevalence of HPV5 ($p < 0.001$), however, but not HPV36 and HPV38 in skin lesions of patients subjected to PUVA therapy. Given the high overall prevalence of HPV5 (89%) it probably would have been impossible for Favre *et al* (1998a,b) to reveal a statistically significant increase following PUVA treatment. The HPV5 data could be reconciled by assuming a higher load of viral DNA in PUVA-treated patients and differences in the sensitivity of HPV5 detection in both studies.

Our data may indicate that photochemotherapy selectively favors the replication of specific HPV types. In line with this hypothesis, HPV5 DNA was detected in three of four patients subjected to long-term, high-dose PUVA therapy (2000–3600 J per cm²). It is interesting to note that HPV8, which is a close relative of HPV5 and known for its association with skin cancer in EV, was detected twice in this patient group only. Coinciding with the preferential detection of high-risk EV-HPV, two of the HPV5 positive patients developed multiple squamous and basal cell carcinomas, which were unfortunately not available for DNA analysis. HPV5 positive, PUVA-associated nonmelanoma skin cancers, however, have been described in psoriasis patients treated with high doses of UVA (Bayle-Lebey *et al*, 1994; Harwood *et al*, 1998). There is clear evidence that PUVA is a risk factor for skin cancer in psoriasis patients. Apart from chemical cross-linking of DNA by psoralen and subsequent UVA irradiation, light sources used in PUVA therapy also emit a small but significant wavelength component in

the UVB region and both, UVA and UVB were shown to induce p53 mutations (Nataraj *et al*, 1997). PUVA treatment also behaves as an immunosuppressive in the skin. This may well offer another explanation for the increased incidence of carcinomas in PUVA-treated patients (Morison *et al*, 1998). Our data on increased prevalence of high-risk EV-associated HPV following high-dose PUVA therapy may suggest that these types further contribute to cancer development.

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