

## MINIREVIEW

# Heterogeneity of the Human Papillomavirus Group

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Almost 70 years have elapsed between the discovery of the infectious nature of human papillomas (9) to the establishment of papillomaviruses as a heterogeneous group (30, 31, 50). The acquisition of detailed information was hampered by the lack of an adequate *in vitro* system to propagate human papillomaviruses.

To date, 60 different types of human papillomaviruses (HPVs) have been isolated and characterized with the help of cloning systems in bacteria. In the majority of isolates, characterization has been based solely on the description of the DNA genome and its comparison to other known HPV prototypes. At one of the first international workshops on papillomaviruses (10), it was decided that a new type of HPV will be defined as an ~7.9-kilobase closed circular, double-stranded DNA molecule which, by using liquid hybridization under stringent conditions, shows less than 50% homology to any of the known HPVs.

The molecular organization of the HPV DNA genomes was defined on a comparative basis with that of the well-characterized bovine papillomavirus type 1 (BPV-1) genome (8). Data on the latter were much more readily obtainable because of the easy accessibility of BPV particles from lesions of experimentally infected animals. After subsequent sequencing of the BPV-1 genome, different genes were determined according to the open reading frames available. By means of colinear DNA comparisons and subsequent DNA sequencing, a genome organization for HPV analogous to that of BPV DNA was established. Although minor variations do occur, the HPVs all contain at least seven so-called early genes (E1 to E7) and two late genes (L1 and L2). In addition, an upstream regulatory region harbors the regulatory sequences which appear to control most transcriptional events of the HPV genome. The function of the E6 and E7 genes of, e.g., HPV-16 and HPV-18 has been studied in great detail. These studies established the role of these gene functions in transforming specific rodent cells and in immortalizing human keratinocytes (6, 63, 64). The E4 gene seems to exert a late function in the viral replication cycle (19).

HPVs have in the past conveniently been grouped together into those associated with lesions of mucosal origin and those mainly found in cutaneous lesions. Apart from HPV-1 and HPV-4 (verrucae plantares and verrucae vulgares), HPV-3 (verrucae planae), HPV-7 (butchers' warts), and a few rare HPV types, the majority of the HPVs associated with skin lesions have been described in and isolated from lesions of patients suffering from a rare hereditary disease, epidermodysplasia verruciformis (EV). Of these HPVs, HPV-5 and HPV-8 (and to a lesser extent HPV-14, HPV-17, and HPV-20) have been associated with squamous cell carcinomas developing in these patients usu-

ally at sunlight-exposed sites (48, 56). These types have also been found in skin carcinomas in patients receiving renal allografts (2). Another type associated with some cutaneous squamous cell carcinomas is HPV-41 (33). This virus has not yet been isolated from patients with EV.

The papillomaviruses predominantly associated with mucosal lesions include those found in benign and malignant lesions of the genital tract. Of these, some are found mainly in malignant lesions, e.g., HPV-16 and HPV-18, whereas others are more common in benign lesions, e.g., HPV-6, HPV-11, and HPV-42. This does not appear to be a useful approach to the classification of these viruses, since many of these types have been described in benign as well as in malignant tumors.

Although a number of so-called genital HPVs have subsequently been described in tumors of the respiratory and digestive tract, the majority of the malignant lesions in this area remain thus far negative for the presence of HPV DNA of defined types. The only two HPVs exclusively demonstrated in the oral mucosa are HPV-13 (57) and HPV-32 (5). HPV-13 has only been found in focal epithelial hyperplasia (FEH), whereas HPV-32 was detected in similar lesions, as well as in an oral papilloma.

An HPV type which can be demonstrated in mucosal as well as in cutaneous lesions is represented by HPV-57. Other exceptions to a strict cutaneous versus mucosal classification follow. (i) HPV-2, which is closely related to HPV-57 and associated with hand warts, has been also demonstrated in oral lesions (16, 18). (ii) HPV-7, which is found in hand warts of patients handling meat (52), has frequently been isolated specifically from oral papillomas of patients infected with human immunodeficiency virus (32a). (iii) HPV-16, the virus most commonly associated with the etiology of genital intraepithelial neoplasias and cervical carcinomas, has been isolated from a number of Bowen's disease lesions of the skin (53; de Villiers, unpublished data). This viral DNA has additionally been found in individual cases of other skin lesions, such as an epidermal nevus (15).

Table 1 lists the 60 HPV types characterized until now. Predictably, this number will increase very rapidly with new isolations that show, as in the past, a larger or lesser degree of homology to one or more of the known HPV prototypes. The present mode of isolation of new HPV types relies on cross-reactivity with established prototypes under hybridization conditions of low stringency. This procedure renders it difficult to isolate putative new HPV types that are only distantly related to those known today. The isolation and characterization of HPV-41, which has very little homology to other HPV DNA, directly from viral particles stresses the possible existence of such distantly related viruses. HPV-41

TABLE 1. HPV types characterized to date<sup>a</sup>

HPV type	Location	Isolated from	Associated with	Homology <sup>b</sup> with type (%)	Genome length <sup>c</sup>	Source or reference <sup>d</sup>
1	Cutaneous	Verruca plantaris	Verruca plantaris		7,815	25, 35, 13
2	Cutaneous	Verruca vulgaris	Verruca vulgaris; verruca plantaris	57 (17)	ca. 7,900	50, 35
3 <sup>e</sup>	Cutaneous	Verruca plana	Verruca plana	10 (34)	ca. 7,800	51, 41
4	Cutaneous	Verruca vulgaris	Verruca vulgaris; verruca plantaris		ca. 8,000	30, 35
5	Cutaneous	Pityriasis versicolor-like macular lesions of EV	EV (benign) EV (squamous cell carcinoma)	8 (17) (76) <sup>f</sup> 9 (4) 12 (30)	7,746	51, 40, 65
6 <sup>e</sup>	Genital mucosa	Condyloma acuminatum	CIN Laryngeal papilloma Buschke-Löwenstein tumors	11 (25) (82) <sup>f</sup> 13 (4)	7,902	32, 17, 60
7	Cutaneous	Butchers' wart	Butchers' wart	40 (13)		52, 47
8	Cutaneous	Macular lesions (EV)	EV (benign) EV (squamous cell carcinomas)	5 (16) (76) <sup>f</sup> 12 (28)	7,654	49, 58, 26
9	Cutaneous	EV lesions	EV (benign)	5 (4)	ca. 7,200	49, 40
10 <sup>e</sup>	Cutaneous	Verruca plana	Verruca plana	3 (32)	ca. 7,600	51, 41
11 <sup>e</sup>	Genital mucosa	Laryngeal papilloma	CIN Laryngeal papilloma	1 (53) <sup>f</sup> 6 (25) (82) <sup>f</sup> 13 (3) 16 (59) <sup>f</sup>	7,931	29, 29
12	Cutaneous	Macular lesions (EV)	EV (benign)	5 (20) 8 (23)	ca. 7,800	49, 41
13	Oral mucosa	FEH (morbus Heck)	FEH	6 (4) 11 (3)	ca. 7,800	57
14	Cutaneous	Flat warts (EV)	EV (benign) EV (squamous cell carcinoma)	5 (13) 8 (10) 9 (3) 12 (9) 19 (14) 20 (32) 21 (32) 22 (10) 23 (24)	ca. 7,700	39
15	Cutaneous	Flat warts (EV)	EV (benign)	5 (3) 9 (8) 17 (22)	ca. 7,200	39
16	Genital mucosa	Cervical carcinoma	CIN; cervical carcinoma		7,905	20, 61
17	Cutaneous	Macular lesions (EV)	EV (benign) EV (squamous cell carcinoma)	9 (8) 14 (2) 15 (20)	ca. 7,200	39
18	Genital mucosa	Cervical carcinoma	CIN; cervical carcinoma	2 (reference 7)	7,857	7, 11
19	Cutaneous	Macular lesions (EV)	EV (benign)	5 (7) 14 (21) 20 (8) 21 (9) 22 (16) 23 (28) 25 (25)	ca. 7,700	39
20	Cutaneous	Flat warts (EV)	EV (benign) EV (squamous cell carcinoma)	5 (10) 14 (29) 19 (6) 21 (25) 22 (14) 23 (14) 24 (4)	ca. 7,700	39
21	Cutaneous	Flat warts (EV)	EV (benign)	5 (11) 14 (39) 17 (3) 19 (6) 20 (38) 22 (10) 23 (19)	ca. 7,700	39
22	Cutaneous	Macular lesions (EV)	EV (benign)	5 (7) 14 (7) 19 (17) 20 (7) 21 (11) 23 (18)	ca. 7,200	39

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TABLE 1—Continued

HPV type	Location	Isolated from	Associated with	Homology <sup>b</sup> with type (%)	Genome length <sup>c</sup>	Source or reference <sup>d</sup>
23	Cutaneous	Macular lesions (EV)	EV (benign)	5 (10) 22 (21)	ca. 7,200	39
24	Cutaneous	Macular lesions (EV)	EV (benign)	5 (2) 14 (3) 20 (4)	ca. 7,700	39
25	Cutaneous	Macular lesions (EV)	EV (benign)	5 (29) 8 (29) 9 (4) 19 (25)	ca. 7,700	28
26	Cutaneous	Verruca vulgaris (immunosuppressed patient)		51 (<10)	ca. 7,800	55
27	Cutaneous	Verruca (immunosuppressed patient)		57 (25) 2		54
28	Cutaneous	Verruca plana				22
29	Cutaneous	Verruca vulgaris				21
30	<b>Genital and oral mucosa</b>	<b>Laryngeal carcinoma</b>	<b>CIN</b>	<b>53 (25)</b>	<b>ca. 7,800</b>	<b>36</b>
31	<b>Genital mucosa</b>	<b>CIN</b>	<b>CIN; cervical carcinoma</b>	<b>16 (35 to 40)</b>		<b>42</b>
32	Oral mucosa	FEH	FEH Oral papilloma	13 (2) 18 (4)	ca. 7,800	5
33	<b>Genital mucosa</b>	<b>Cervical carcinoma</b>	<b>CIN</b> <b>Cervical carcinoma</b>	<b>16</b> <b>52 (28)</b> <b>58 (&lt;10)</b>	<b>7,909</b>	<b>3, 12</b>
34	Genital mucosa (cutaneous)	Bowen's disease (cutaneous)	CIN (genital)		ca. 7,660	38
35	<b>Genital mucosa</b>	<b>Cervical adenocarcinoma</b>	<b>CIN; cervical carcinoma</b>		<b>7,850</b>	<b>43</b>
36	Cutaneous	Actinic keratosis	EV (benign)	5 (30) 8 (24) 19 (7) 15 (21) 17 (19)	ca. 7,900	37
37	Cutaneous	Keratoacanthoma			ca. 7,800	59
38	<b>Cutaneous</b>	<b>Malignant melanoma</b>			<b>ca. 7,800</b>	<b>59</b>
39	<b>Genital mucosa</b>	<b>PIN</b>	<b>CIN; cervical carcinoma</b>		<b>ca. 7,900</b>	<b>4</b>
40	Genital mucosa	PIN	CIN	7 (13)	ca. 8,000	17a
41	<b>Cutaneous</b>	<b>Disseminated warts</b>	<b>Cutaneous squamous cell carcinoma</b>		<b>ca. 7,500</b>	<b>33</b>
42	Genital mucosa	Vulvar papilloma	CIN	32 (20)	ca. 7,900	4
43	Genital mucosa	Vulvar hyperplasia	CIN (normal cervical mucosa)		ca. 7,600	42a
44	Genital mucosa	Vulvar condyloma	CIN (normal cervical mucosa)	13 (20)	ca. 7,800	42a
45	<b>Genital mucosa</b>	<b>CIN</b>	<b>CIN; cervical carcinoma</b>	<b>18 (25)</b>	<b>ca. 8,000</b>	<b>45</b>
46	Cutaneous	Macular lesions (Hodgkin's disease patient)	EV (benign)	14 (23)	ca. 7,900	34
47	Cutaneous	Macular and verrucae lesions (EV)	EV (benign)	5 (2 to 9)	ca. 7,700	1
48	<b>Cutaneous</b>	<b>Cutaneous squamous cell carcinoma (transplant patient)</b>			<b>ca. 7,200</b>	<b>44</b>
49	Cutaneous	Verruca plana (immunosuppressed patient)				23
50	Cutaneous	EV (benign)				24
51	<b>Genital mucosa</b>	<b>CIN</b>	<b>CIN; cervical carcinoma</b>	<b>26 (&lt;10)</b>	<b>ca. 8,000</b>	<b>46</b>
52	<b>Genital mucosa</b>	<b>CIN</b>	<b>CIN; cervical carcinoma</b>	<b>33 (28)</b>	<b>ca. 8,000</b>	<b>62</b>
53	Genital mucosa	Normal cervical mucosa		30 (25)	ca. 8,000	27
54	Genital mucosa	Condyloma acuminatum				D. Kremsdorf, personal communication
55	Genital mucosa	Bowenoid papulosis				M. Favre, personal communication
56	<b>Genital mucosa malignant potential</b>	<b>CIN; cervical carcinoma</b>	<b>CIN</b>			<b>A. T. Lorincz, personal communication</b>
57	Oral and genital mucosa (cutaneous)	Inverted papilloma of the maxillary sinus	CIN Verruca vulgaris	2 (17) 27 (25)	ca. 8,000	17a

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TABLE 1—Continued

HPV type	Location	Isolated from	Associated with	Homology <sup>b</sup> with type (%)	Genome length <sup>c</sup>	Source or reference <sup>d</sup>
58	Genital mucosa	CIN		33 (<10)		T. Matsukura, personal communication
59	Genital mucosa	Vulvar intraepithelial neoplasia			ca. 8,000	Matsukura, personal communication
60	Cutaneous	Epidermoid cyst			ca. 8,000	Matsukura, personal communication

<sup>a</sup> Boldface type indicates that the HPV types are predominantly associated with malignant tumors. CIN, Cervical intraepithelial neoplasia; PIN, penile intraepithelial neoplasia.

<sup>b</sup> Determined by reassociation kinetics.

<sup>c</sup> If sequenced, the exact nucleotide number is given, but if determined by agarose gel electrophoresis, the estimated length is given.

<sup>d</sup> The first source or reference listed is to the first description of the virus, the second reference is to the cloning of the virus, and the third reference is to the sequence description, if done.

<sup>e</sup> On rare occasions, also found in malignant tumors.

<sup>f</sup> Determined by nucleotide sequence comparison.

cannot be classified with any of the other HPVs when relatedness on the DNA sequence level is compared.

Several HPV genomes (types 1, 5, 6, 8, 11, 16, 18, 31, 33, and 52) have been sequenced or are in the process of being sequenced. It seems likely that sequencing of all described HPV types will provide a new baseline for a reclassification of this family of viruses.

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