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Different skin wart types, different human papillomavirus types? A narrative review

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Abstract

Skin warts are ubiquitous, self-limiting, benign neoplasms caused by human papillomaviruses (HPV). Several studies have investigated the prevalence and diversity of HPV types in the three main types of skin warts: common, plantar, and flat warts. Using different methodological approaches and diverse populations, several HPV types were detected in skin warts, but often the etiological link remained unconfirmed. This review addresses recently improved multiple strategies for investigating the presence of HPVs in skin warts, covering proper sampling techniques for HPV testing, choice of molecular method(s) for HPV detection, and assignment of the etiological causality of the tested skin wart to a causative HPV type using cellular viral load estimation. These novel approaches provide useful insight into the range of HPV types causing skin warts and support a refined understanding of their etiology. In addition, we conducted a literature review of the main studies examining HPV prevalence and genotype distribution in common warts, plantar warts, and flat warts. Finally, HPV type-specific histopathological patterns in skin warts are briefly discussed.

Keywords: skin warts, human papillomaviruses, HPV, detection, prevalence, etiology

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Introduction

Skin warts are ubiquitous, benign, self-limiting neoplasms of the cutaneous stratified squamous epithelia that pose a significant public health problem due to their high incidence, often long-term persistence, and the various forms of discomfort and pain they can cause (1–3). In general, skin warts present clinically as single or multiple keratotic papules of varying sizes with a rough or smooth surface and exophytic, endophytic, or flat-topped growth (4, 5). Skin warts can occur in people of all ages, especially on exposed areas of the body, such as the fingers, hands, feet, elbows, knees, and face (5). There are three main types of skin warts in the general population: common warts (*verrucae vulgares*), plantar warts (*verrucae plantares*), and flat warts (*verrucae planae*), usually diagnosed based on their clinical and dermoscopic features and anatomical localization (Figs. 1, 2, and 3) (6–8). Although skin warts are usually diagnosed clinically, dermoscopy is an indispensable adjunct non-invasive point-of-care tool that offers improved diagnostic accuracy of skin warts compared to the clinical diagnosis (9) and sometimes also differentiation between various types of skin warts (Figs. 4, 5, and 6). Although not specific, skin warts usually present with dermoscopic features such as papillomatous growth, dotted vessels, linear vessels, and bleeding (6).

The etiology of skin warts is related to productive infection of the epidermis by different types of human papillomaviruses (HPV), a diverse group of small, non-enveloped DNA viruses from the *Papillomaviridae* family (10, 11). As of November 7th, 2023, 225 HPV types have been officially recognized and are classified into five different viral genera: *Alphapapillomavirus* (*Alpha*-PV), *Betapapillomavirus* (*Beta*-PV), *Gammapapillomavirus* (*Gamma*-PV), *Mupapillomavirus* (*Mu*-PV), and *Nupapillomavirus* (*Nu*-PV) (10, 12). Several cutaneous HPV types from the *Alpha*-, *Gamma*-, *Mu*-, and *Nu*-PV genera are often etiologically associated with the development of various types of skin warts, regardless of the immune status of the patients (7, 13). Meanwhile, HPV types from the *Beta*-PV genus usually cause only asymptomatic infections of healthy skin and hair follicles in immunocompetent individuals (14) and have been associated with the development of numerous persistent, flat wart-like skin neoplasms in individuals with an iatrogenically or genetically compromised immune system, such as in patients with the rare inherited disease epidermodysplasia verruciformis, in which they can subsequently develop into cutaneous squamous cell carcinomas when exposed to ultraviolet radiation (5, 15, 16).

Skin infection with HPV requires the inoculation of viral particles—virions—into the basal cells of the epidermis, most commonly through preexisting skin microinjuries, where the virus forms a reservoir with a low level of viral genome replication. Due to the effect of the viral proteins on the regulation of the cell cycle, the infected suprabasal epithelial cells proliferate more than under normal physiological conditions, leading to the formation of a wart. As the infected epithelial cells differentiate and progress to higher layers of the epidermis, the replication capacity of HPV increases and a large number of new mature virions are produced and released from the superficial epithelial layer (7, 11). HPV virions can be further transmitted through direct contact with an infected part of the epidermis or indirectly through HPV-contaminated surfaces and objects, with reinfection and autoinoculation being very common, especially in children. Depending on the initial concentration of HPV virions at the epidermal infection site, skin warts develop between 3 weeks and 8 months after infection and usually disappear spontaneously within 2 years of their development due to the action of the host's cell-mediated immune response (4, 7, 15), whereas the recurrence of skin warts is often due to the persistence of HPVs in the perilesional skin (17).

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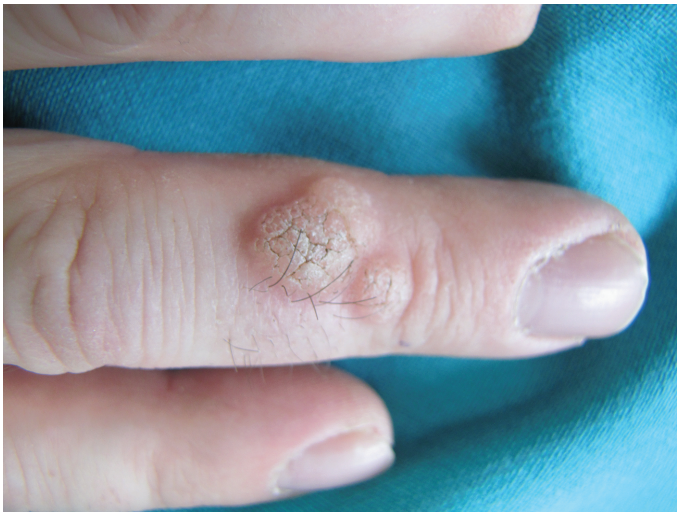

Figure 1 | Macroscopic picture of common warts presenting as exophytic, hyperkeratotic, dome-shaped papules with a rough surface.

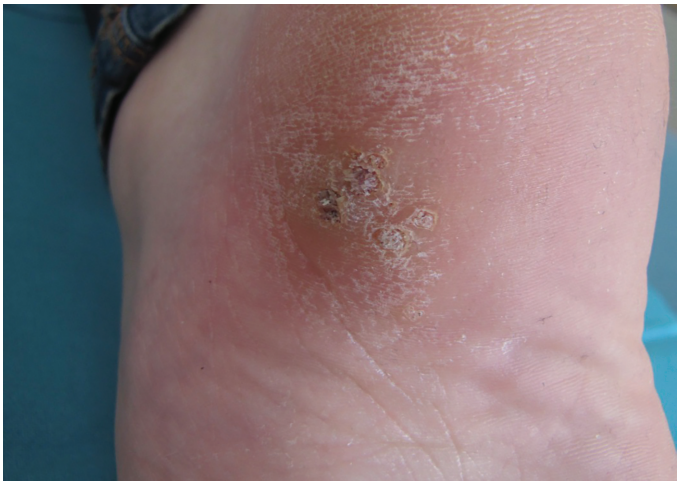

Figure 2 | Macroscopic picture of mosaic type of plantar warts featuring superficial clusters of slightly raised and endophytically growing papules with a rough keratotic surface.

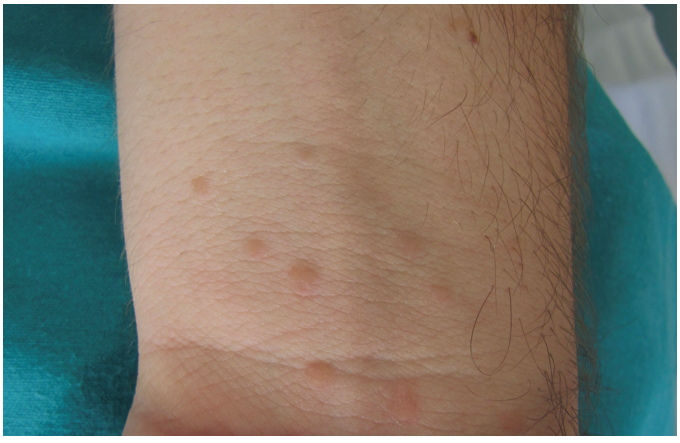

Figure 3 | The macroscopic picture of flat warts typically presents as numerous light brown slightly raised papules with a smooth surface.

Aims of the review

Because cutaneous HPVs are part of the normal skin microbiota (18), an appropriate HPV diagnostic procedure (from sampling to results interpretation) is required to elucidate which of the multiple HPV types detected in an individual skin wart sample is most likely etiologically associated with its development. This review primarily addresses recently improved multiple strategies for investigating the presence of HPVs in the main types of skin warts, covering 1) proper sampling techniques for HPV testing, 2) choice of molecular method(s) for HPV detection, and 3) assignment of the etiological causality of the skin wart to a causative HPV type using cellular viral load estimation. These novel diagnostic approaches provide useful insight into the range of HPV types causing skin warts and support a refined understanding of the etiology of skin warts. In addition, a critical literature review of the main previous studies examining HPV prevalence and genotype distribution in common warts, plantar warts, and flat warts was conducted, and the results are briefly presented. Finally, HPV type-specific histopathological patterns in skin warts are described and discussed.

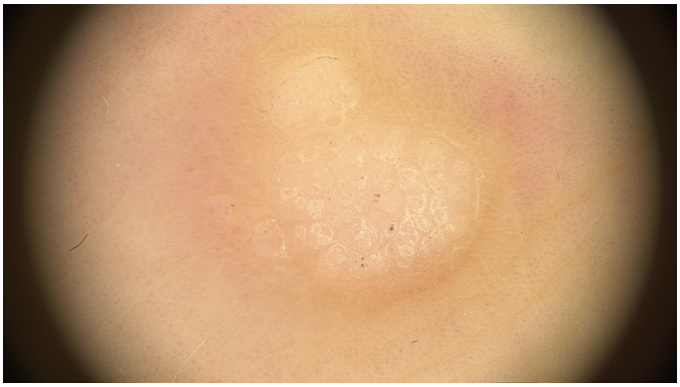

Figure 4 | Dermoscopic picture of a common wart featuring dotted vessels located in the center of the papillae (frog spawn).

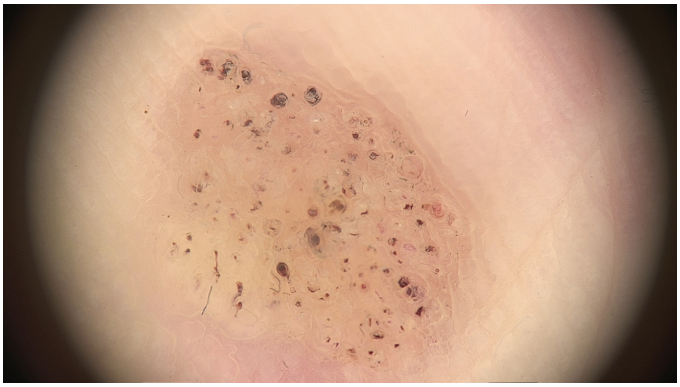

Figure 5 | Dermoscopic picture of a plantar wart typically showing papillomatous growth with brown to red dots and streaks that correspond to hemorrhages.

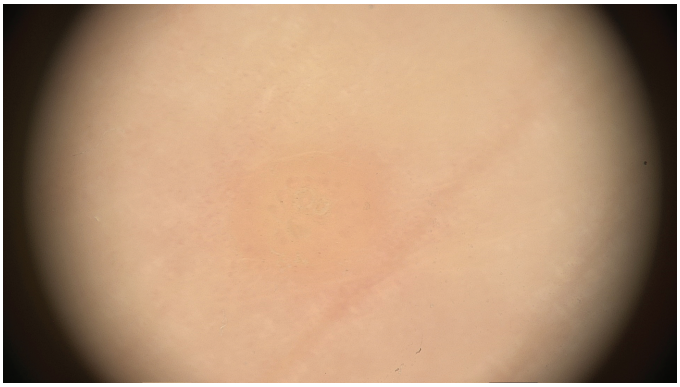

Figure 6 | Dermoscopic picture of a flat wart revealing a yellowish background with delicate papillae and almost invisible dotted vessels.

Sampling of skin warts for HPV testing

In the past, various skin neoplasms such as calluses, corns, seborrheic keratosis, actinic keratosis, lichen planus, knuckle pads, and acral melanoma have occasionally been clinically misdiagnosed as skin warts (8, 19, 20). To avoid possible misclassification, histopathological examination of a tissue sample is an important tool for confirmation of a clinical diagnosis of skin warts, especially in clinically challenging lesions and for research purposes, because it allows detailed differentiation of skin neoplasms based on their morphological features (9, 16). In several previous studies examining the etiology of skin warts, they were only diagnosed clinically prior to HPV testing (21–26), and so possible clinical misclassification could be the reason why HPV DNA was not detected in some skin warts (27). Thus, in our opinion only samples of histologically confirmed skin warts should be used in studies examining HPV prevalence, HPV genotype distribution, and the etiology of skin warts.

To detect HPVs in skin warts, skin swabs of the wart's surface have often been used as clinical samples (2, 22–24, 26), which are non-invasive and painless to collect and have been shown to be sensitive and efficient for HPV detection, but only provide information on the presence of the virus(es) in the superficial layers of the warts (26, 28, 29). Because cutaneous HPVs are also part of the normal skin microbiota (18), previous work has confirmed the presence of HPV DNA in up to 84% of swab samples from clinically normal skin, raising the question of whether the identification of HPVs on the surface of skin warts is the result of contamination, colonization, latent infection, or productive infection (causing the development of warts) (28, 30–32). Although a skin biopsy is a more invasive clinical sampling method than skin swabs, it provides important information on the localization of HPV DNA throughout the thickness of the neoplasm and has therefore been recommended as the standard for research on the etiology of skin warts (16, 28, 33, 34). Forslund et al. (28) have additionally demonstrated that repeated tape-stripping of the surface of skin neoplasms prior to biopsy sampling effectively removes the superficial epithelial cells (and associated microbial flora, including HPV) without affecting the histopathological morphology of the lower epithelial layers and significantly reduces the prevalence of potentially contaminating (resident) HPVs from the surrounding area. In studies on the presence of HPV in skin warts, scraping hyperkeratotic scales (26, 29) and skin microbiopsy (35) were also used as less invasive clinical sampling methods than traditional skin biopsy and proved to be useful for HPV detection.

In addition to the choice of sampling method, the duration of the clinical presentation of sampled skin warts is an important factor for the efficiency of further HPV detection because the probability of detecting HPV DNA in a wart's tissue decreases with the duration of its clinical presentation (2).

Choice of molecular method(s) for HPV detection in skin warts

When investigating the presence of HPVs in skin warts, the most commonly used molecular methods are HPV type-specific quantitative real-time polymerase chain reaction (PCR) (3, 32, 33, 36) and PCR using various broad-spectrum primers (e.g., MY09/11 and RK91, FAP59/FAP64, HVP2/B5, LR-α-HPV FW/RW, *Gamma*-PV-E1F/E1R, and a collection of CP, CN, and SK primers) targeting the most conserved viral genomic regions—L1 or E1 open reading frames—to detect a larger group of phylogenetically closely related HPV types, followed by Sanger sequencing of the PCR products (3, 17, 21, 24, 26, 32, 37–40) or hybridization with type-specific oligonucleotide probes for HPV typing (22, 23, 25). Other methods used to detect HPVs in skin wart samples were restriction enzyme cleavage of PCR products (25, 38, 41–43), Southern blot hybridization (13, 41), and *in situ* hybridization (13, 44), which tend to be less sensitive and specific in HPV typing (37, 44). Recently, a rapid and accurate HPV-specific detection system using colorimetric loop-mediated isothermal amplification (LAMP) in combination with microfluidic technology has also been developed to detect cutaneous HPVs in skin warts, and it has been shown to have higher sensitivity and suitable specificity compared to the conventional sequencing of PCR products (45). The method of next-generation sequencing (NGS), which allows the identification of different nucleic acids regardless of the knowledge of their nucleotide sequences (34), has shown that several potentially new cutaneous HPV types may be present in skin wart samples (46).

Assigning the etiological causality of the skin wart to a causative HPV type

Multiple HPV types can be simultaneously detected in individual skin wart samples (1, 17, 39), which makes it difficult to assign the etiological causality of the particular skin wart to a specific (causative) HPV type. Using the laser capture micro-dissection method combined with HPV PCR typing, it was previously demonstrated that only one HPV type is present in a single defined cervical intraepithelial neoplastic lesion (47). The results led to the establishment of the "one virus, one lesion" concept, according to which only a single HPV type is etiologically associated with the development of a specific neoplasm (23, 47), whereas the other HPV types are most likely present due to contamination of the surface of the neoplasm tested (28) or as innocent HPV bystanders with no clear active biological role and no significant tissue damage as a result of their replication (18, 32). In several studies on the prevalence of HPVs in skin warts, the authors focused primarily on investigating the diversity of cutaneous HPV types detected and often evaluated the possible etiological agents of skin warts based only on their high prevalence rate, without reliably determining the presumed etiological link (17, 21, 23–26, 39, 40, 43).

To determine the etiological role of HPVs in the development of a particular skin wart, it has been proposed to estimate the cellular viral load of all HPV types detected in a given wart sample using highly sensitive HPV type-specific quantitative PCR (qPCR) assays coupled with the human beta-globin qPCR assay (3, 32, 33, 36). Köhler et al. (33) have shown in dermoscopically confirmed common and plantar warts of immunocompetent patients that the viral load of wart-associated HPV27 and HPV57 (the *Alpha*-PV genus) was up to 3.5×10^5 and 3.0×10^5 viral copies per cell, respectively, indicating productive viral infections and the etiological role of both HPV types in the development of skin warts. In contrast, the viral load of cutaneous HPV types from the *Beta*-PV genus, which only cause asymptomatic infections in immunocompetent patients, was between 1.0×10^{-4} and 5.7×10^{-1} viral copies per cell. In addition, the viral load of HPV27 in common and plantar warts in immunocompromised patients was up to 1.6×10^5 viral copies per cell, confirming an active biological role of the virus in skin wart development, regardless of the immune status (33).

Based on a clear bimodal distribution of cellular viral loads of

HPV2, HPV27, and HPV57 from the *Alpha*-PV genus and HPV1 and HPV63 from the *Mu*-PV genus in histologically-confirmed common wart samples containing a single HPV type (between 5.0×10^{-4} and 7.1×10^{6} viral copies per cell), we established the robust cutoff value of one viral copy per cell for distinguishing between causative and non-causative HPVs or HPV bystanders (32). The estimated viral load confirmed that the causative HPV types in successfully etiologically characterized common warts (79.8% of sampled skin warts) in immunocompetent patients were HPV57 (in 43.5% of samples), HPV27 (22.6%), HPV2 (9.7%), and HPV1 (4.0%), whereas no significant differences in their viral load were found in samples containing single or multiple HPV types (32). In all patients from whom multiple common warts were sampled, there was complete concordance of the assigned causative HPV types in the different wart samples, confirming previous observations that a single HPV type is usually involved in the development of multiple skin warts in an individual patient, most likely due to autoinoculation (23, 32).

Using the improved diagnostic protocol to comprehensively characterize the etiological agents of skin warts based on the estimation of cellular viral load and the applied cutoff value for causal determination (3, 32), a total of 12 different causative HPV types were subsequently identified in 95.3% of histologically confirmed common warts in immunocompetent patients, with HPV27 being the most frequent (in 27.0% of samples), followed by HPV57 (26.2%), HPV4 from the *Gamma*-PV genus (15.1%), HPV2 (13.5%), and HPV65 from the *Gamma*-PV genus (7.9%). To a lesser extent, HPV1 and HPV3, HPV7, HPV10, HPV28, and HPV29 (the *Alpha*-PV genus) and HPV95 (the *Gamma*-PV genus) were also characterized as causative HPV types of common warts (3). In accordance with the "one virus, one lesion" concept (23, 47), the single causative HPV type was reliably identified in all common warts with successful etiological characterization, including samples containing multiple HPV types (3). It was also shown that the measured cellular viral loads of HPV4 and HPV65 (between 1.7×10^{2} and 6.8×10^{5} viral copies per cell) were significantly higher than the viral loads of HPV2, HPV27, and HPV57 (between 1.1×10^{0} and 5.5×10^{5} viral copies per cell) in the common warts caused. In addition, HPV65 was etiologically associated with the development of common warts in significantly older patients than HPV27 and HPV57, whereas HPV4-induced common warts were significantly smaller than warts caused by HPV2, HPV27, HPV57, and HPV65 (3).

HPV prevalence and genotype distribution in skin warts: literature review

Common warts

Common warts are the most frequent and best-studied type of skin warts. They can develop in people of all ages, but they are more frequent in children and adolescents (5). Common warts usually appear as single or multiple neoplasms ranging in size from 1 to over 10 mm on exposed areas of the body such as the fingers, hands, elbows, knees, and face. The characteristic clinical picture of common warts consists of grayish-brown, exophytic, hyperkeratotic, dome-shaped papules with a rough surface, whereas warts in the periorificial areas often have a filiform appearance (Figs. 1 and 4) (5, 7).

Studies have shown that HPV27 (in 20.8%–31.7% of samples tested), HPV57 (12.4%–35.2%), HPV2 (10.4%–34.7%), HPV1 (3.3%–31.3%), and HPV4 (1.8%–19.8%) are the most frequent HPV types detected in samples of common warts worldwide (Fig. 7) (2, 3, 17, 23–25, 39, 42). Meanwhile, HPV7 from the *Alpha*-PV genus is mainly found in the butcher's wart variant, which has a cauliflower-like appearance and often develops in people whose skin is chronically macerated due to moisture and cold, such as meat handlers and fishmongers (4, 15). It has been suggested that the extremely variable detection rates of HPV types in common warts in the published data may be due to differences in the sensitivity and specificity of broad-spectrum primers used for HPV detection and to the populations studied from various geographical regions (21, 25, 37, 38). Hagiwara et al. (21) showed that HPV1 (in 44.1% of samples), HPV4 (16.4%), and HPV65 (14.1%) predominated in common warts in the Japanese population, whereas HPV2 (6.1%), HPV27 (6.1%), and HPV57 (4.7%) were identified in a much lower proportion.

In immunocompromised individuals such as organ transplant patients and patients infected with human immunodeficiency virus (HIV), skin warts occur more frequently and in greater numbers and are more resistant to treatment (5, 7, 8, 37). Previous studies have shown that HPV2, HP27, and HPV57 can also be detected in the most common warts of renal transplant recipients and HIV-positive patients (37, 38), confirming that the distribution of wart-associated HPV types in skin warts is mainly independent of the host's immune system (41), whereas the diversity of other cutaneous HPV types tends to be higher in skin warts of immunocompromised patients (37, 46).

Type of skin wart	HPV type*
Common warts	**HPV27**, **HPV57**, **HPV2**, HPV1, HPV4
Plantar warts	**HPV57**, **HPV2**, **HPV27**, HPV1, HPV4, HPV66, HPV60, HPV65, HPV63
Flat warts	**HPV3**, **HPV10**, HPV26, HPV27, HPV28, HPV29, HPV77, HPV78, HPV94, HPV117, HPV41

Figure 7 | The most prevalent types of human papillomaviruses (HPV) in common warts, plantar warts, and flat warts in the immunocompetent population. *The font size of the HPV types is in weighted proportion to their prevalence rate, with the lowest value in the published data being taken into account. The color of the HPV type indicates the viral genus (red = *Alphapapillomavirus*, blue = *Betapapillomavirus*, green = *Mupapillomavirus*, orange = *Nupapillomavirus*).

Plantar warts

Plantar warts account for about one-third of all skin warts and usually appear as hyperkeratotic papules of various shapes on the soles of the feet of children, adolescents, and adults (Figs. 2 and 5) (5, 7). Depending on the clinical appearance, plantar warts can mainly be divided into different subtypes: 1) mosaic plantar warts, which develop as superficially growing and slightly raised clusters of papules with a rough surface, confluent growth, and a characteristic keratinaceous plug surrounded by a hard hyperkeratotic rim, and 2) deep plantar warts (myrmecia), which mainly occur in children between 5 and 15 years old as endophytic growing, deep, smooth-surfaced, single papules at the pressure points on the feet, causing pain especially when walking (5, 15, 48, 49).

The most common HPV types detected in plantar warts are HPV57 (in 15.6%–37.1% of samples tested), HPV2 (9.3%–26.7%), HPV27 (8.9%–49.5%), HPV1 (6.7%–28.8%), and HPV4 (5.5%–6.0%), whereas HPV66 from the *Alpha*-PV genus, HPV60 and

HPV65 from the *Gamma*-PV genus, and HPV63 from the *Mu*-PV genus were reported with lower frequency (Fig. 7) (7, 17, 23, 24, 26, 40). Previous work has shown that HPV1 has a distinct clinical profile because it is usually detected in deep plantar warts that occur in primary care patients, especially in children under 12, and can regress relatively quickly (in less than 6 months) without treatment (23, 31). Meanwhile, HPV2, HPV27, and HPV57 are commonly detected in mosaic plantar warts, which are notorious for their longevity and resistance to treatment (2, 7, 49, 50).

Similar to common warts, immunocompromised patients have been observed to have a significantly greater number of plantar warts as well as longer duration, higher treatment resistance, and greater frequency of recurrence (50, 51). King et al. (50) have confirmed that HPV2, HP27, and HPV57 can also frequently be detected in plantar warts of HIV-positive patients.

Flat warts

Flat warts, also known as plane warts, account for about 4% to 8% of skin warts and usually develop on the dorsum of the hands, distal forearms, face, and ankles, particularly in children and adolescents. Clinically, flat warts appear as numerous, scattered, light brown or skin-colored, slightly raised papules with irregular outlines and a smooth surface between 2 and 4 mm in size. Flat warts often occur in areas where the skin has been traumatized (Koebner phenomenon) (5, 7, 49). In general, flat warts have the highest rate of spontaneous regression among cutaneous HPV infections because they usually disappear within a few weeks or months, often accompanied by pruritus, superficial swelling, or depigmented halos (7).

The HPV types most commonly detected in flat wart samples are HPV3 and HPV10 from the *Alpha*-PV genus, but occasionally also HPV26, HPV27, HPV28, HPV29, HPV77, HPV78, HPV94, and HPV117 from the *Alpha*-PV genus and HPV41 from the *Nu*-PV genus in lower frequencies (Fig. 7) (7, 24, 25, 43).

HPV-type specific histopathological patterns in skin warts?

Histopathological examination is crucial for the diagnostic confirmation of skin warts, especially when their clinical appearance is atypical (8, 9). Histologically, skin warts typically show prominent folding of the epithelial basal layer, or *stratum basale*, with hyperplasia and enlargement of contiguous dermal papillae (papillomatosis) and generalized enlargement of the epithelial cells (hypertrophy) leading to thickening of the spinous layer, or *stratum spinosum* (acanthosis), and the outermost, cornified layer, or *stratum corneum* (hyperkeratosis). The epithelial cells within the cornified layer often retain nuclei (parakeratosis) (4, 7). Whereas the above histopathological features are not only associated with HPV infections (7), epithelial cells in the spinous layer and granular layer, or *stratum granulosum*, of skin warts often contain abundant intracytoplasmic and, less frequently, intranuclear inclusion bodies of characteristic appearance, which are classified as cytopathogenic effects because the viral protein E4 in particular accumulates in them as a consequence of productive infection with certain HPV types (52).

A few studies have described the occurrence of HPV type-specific histopathological patterns in skin warts; for example, HPV1 was found to be associated with the formation of a granular type of intracytoplasmic inclusion bodies, and HPV4, HPV60, and HPV65 were associated with a homogeneous type and HPV63 with a filamentous type of inclusion bodies (53). In contrast, such intracytoplasmic inclusion bodies are usually not present in epithelial cells of skin warts infected with HPV2, HPV27, and HPV57 (52, 54). As a result of the binding of the viral protein E4 to the cytokeratin network of the cell cytoskeleton and its subsequent destruction, vacuolated epithelial cells with a shrunken and pyknotic nucleus surrounded by a bright band of cytoplasm—a perinuclear halo—appear in the differentiated layers of the epidermis (koilocytosis) (7).

Conclusions

Skin warts are widespread benign skin neoplasms that can occur in people of all ages and whose development is etiologically associated with various HPV types. Several studies have shown that the presence of HPVs can vary among different types of skin warts, but it is usually independent of the patient's immune status. Wart-associated HPV types show various biological differences and cytopathogenic effects that may influence the course and characteristics of skin warts. Because cutaneous HPVs are part of the normal skin microbiota, appropriate sampling protocols, HPV diagnostic methods, and assignment rules for etiological causality of the skin wart to a specific HPV type are required to correctly interpret the detection of multiple HPV types in an individual skin wart sample because only a single HPV type is likely etiologically associated with wart development. Reliable data on the causative agents of skin warts are essential for the development of efficient HPV type-specific treatments for warts, including therapeutic HPV vaccines (1, 36) and an informed choice for the most appropriate target HPV types for prophylactic cutaneous HPV vaccine(s), which would be particularly beneficial for immunocompromised patients with numerous persistent and treatment-resistant skin warts (55). Therefore, in addition to meticulous epidemiological studies on HPV prevalence in skin warts, more basic molecular studies on potential biological differences and immune evasion strategies between different cutaneous HPV types are needed to better evaluate their role in the pathogenesis of skin warts.

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