The Biology and Clinical Features of Cutaneous Polyomaviruses

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Human polyomaviruses are double-strand DNA viruses with a conserved genomic structure, yet they present with diverse tissue tropisms and disease presentations. Merkel cell polyomavirus, trichodysplasia spinulosa polyomavirus, human polyomavirus 6 and 7, and Malawi polyomavirus are shed from the skin, and Merkel cell polyomavirus, trichodysplasia spinulosa polyomavirus, human polyomavirus 6 and 7 have been linked to specific skin diseases. We present an update on the genomic and clinical features of these cutaneous polyomaviruses.


The identification and study of human polyomaviruses (HPyVs) has expanded dramatically in the past decade. The BK and JC PyVs were the first HPyVs discovered and linked to nephropathy and progressive multifocal leukoencephalopathy in 1971 (Gardner et al., 1971; Padgett et al., 1971). Since 2007, starting with KI and WU PyVs, improved technologies have uncovered 10 more possible HPyVs (Allander et al., 2007; Gaynor et al., 2007; Kamminga et al., 2018). Here, we discuss the PyVs shed from human skin, with a particular focus on those linked to disease, including trichodysplasia spinulosa polyomavirus (TSPyV), HpyV6, and HPyV7.

GENOMIC STRUCTURE

Although the overall genomic structure is conserved between cutaneous PyVs, some subtle differences exist (Table 1). Like canonical PyVs, cutaneous PyVs all possess genomes of ~5,000 bp. The PyV genome is divided into early, late, and noncoding control regions. All cutaneous PyV early regions encode for large and small T antigens (LT and ST, respectively).

Early region transcription occurs first, before viral DNA replication. LT alone can replicate the PyV genome. Domains essential for DNA replication are conserved in all cutaneous PyVs, including the DnaJ domain (HPDKGG), Rb/p107/p130 binding motif (LXCE), Zinc-binding (Zn-binding) motif, helicase, and nuclear localization sequence (Table 2) (Borchert et al., 2014; DeCaprio and Garcea, 2013; Van Ghelue et al., 2012). The LXCE and DnaJ/Hsc70 binding motifs work together to bind Rb and disrupt its interaction with E2F to promote cell-cycle progression and viral replication (Sullivan et al., 2000). The Zn-binding motif and helicase domains allow LT to oligomerize and bind viral DNA, unwind it, and recruit host cell DNA replication factors (Zhou et al., 2012). Some PyVs also use the helicase domain to bind and inhibit the p53 tumor suppressor. While HPyV6/7 and Malawi PyV (MWPyV) LTs bind directly to p53 (Berrios et al., 2015; Rozenblatt-Rosen et al., 2012), MCPyV LT inhibits p53 signaling without a direct interaction (Borchert et al., 2014; Cheng et al., 2013). TSPyV LT has also been shown to lack significant interaction with p53 (An et al., 2015). Nonconserved domains in LTs show differences between the cutaneous PyVs (Table 2) (Van Ghelue et al., 2012). MCPyV LT is slightly larger due to an uncharacterized insertion between the DnaJ- and Rb-binding motifs. The LTs of TSPyV, HPyV6/7, and MWPyV, but not MCPyV, possess a motif (WXXWW) that binds the spindle checkpoint protein Bub1. This domain is required for the transforming, but not the immortalizing, properties of SV40 LT (Cotsikis et al., 2004). SV40 LT also promotes transformation through a CUL7-binding motif (FNXEX) in its N-terminus, which is only conserved in TSPyV (Ali et al., 2004).

The ST is generated through alternative splicing and shares the LT DnaJ domain. The C-terminal half of ST possesses two conserved Zn-binding motifs that bind to PP2A isoforms promoting viral DNA replication through multiple mechanisms. The PP2A-binding region of SV40 ST promotes cell-cycle progression (Schuchner and Wintersberger, 1999) and inhibits LT degradation (Scheidtmann et al., 1991), but these activities have not been tested in cutaneous STs. The PP2A binding regions appear to be conserved among cutaneous PyVs (Table 2), MCPyV ST stabilizes LT through a distinct LT stabilization domain motif that is conserved in TSPyV, but not in HPyV6/7 or MWPyV (Table 2) (Kwun et al., 2013). While MCPyV ST can transform primary fibroblasts (Shuda et al., 2011), the transforming properties of other cutaneous STs are unknown.

Some PyVs possess an alternative open reading frame overlapping with LT that encodes for additional protein(s). The TSPyV early region encodes for both middle T antigen and alternative T antigen (Carter et al., 2013; van der Meijden et al., 2015); the MCPyV early region only encodes for alternative T antigen (van der Meijden et al., 2015), while HPyV6/7 and MWPyV encode for neither (Table 1). While the well-characterized mouse PyV middle T antigen is a
phosphorylated membrane protein that alters signaling pathways and promotes transformation, the functions of middle T antigen/alternative T antigen of cutaneous PyVs require further characterization (van der Meijden and Feltkamp, 2018).

MCPyV is the only cutaneous PyV known to encode for a microRNA (Table 1). Like SV40, MCPyV microRNA inhibits LT expression, possibly as a means to limit replication and promote episomal persistence (Seo et al., 2009). More recent LT expression, possibly as a means to limit replication and attenuate the host immune response (Akhbari et al., 2018).

The PyV late genes encode for the capsomere proteins, which surround the viral genome and promote attachment and entry into host cells. Many PyV capsids bind gangliosides terminating in sialic acid as their primary attachment receptor through a structurally conserved groove (Stehle et al., 1994). While MCPyV can bind to ganglioside GT1b (Erickson et al., 2009), glycosaminoglycans have been implicated as the primary entry receptor (Table 1) (Schowalter et al., 2012). More recent structural studies have also demonstrated that the proposed sialic acid binding site is occluded in HPyV6/7, suggesting alternative receptors for cutaneous PyVs (Stroh et al., 2014).

MERKEL CELL POLYOMAVIRUS
MCPyV and its associated disease, Merkel cell carcinoma, have been reviewed extensively elsewhere. Serologic studies indicate that exposure to MCPyV is widespread (DeCaprio, 2017; van der Meijden et al., 2011). Viral DNA is present in 2.6% of healthy blood donors (Mazzoni et al., 2017). Primary exposure to MCPyV begins in childhood after a period of immunity from maternal antibodies (Martel-Jantin et al., 2013; Nicol et al., 2013). Seroprevalence rates rise from early childhood until adulthood, in which 60–96.2% of adult populations are estimated to have had MCPyV exposure (Martel-Jantin et al., 2013; Nicol et al., 2013) (Table 3). MCPyV appears to be the cutaneous PyV most frequently shed from the skin, with studies suggesting shedding from up to 61.5% of healthy individuals (Hampras et al., 2015; Schowalter et al., 2010) (Table 3). An increasing body of research has strongly implicated MCPyV as a cause of its associated carcinoma (DeCaprio, 2017; Feng et al., 2008). Links between MCPyV and other inflammatory or malignant skin conditions remain unconfirmed.

TRICHODYSPLASIA SPINULOSA POLYOMAVIRUS
Case reports in the early 2000s identified a facial, folliculocentric eruption and alopecia in immunosuppressed patients first described as “pilomatrix dysplasia” and later “cyclosporine-induced folliculodystrophy” (Chastain and Millikan, 2000; Haycox et al., 1999; Heaphy et al., 2004; Sperling et al., 2004). While some reports implicated cyclosporine, electron microscopy suggested a viral etiology (Haycox et al., 1999; Sperling et al., 2004). In 2010, van der Meijden and colleagues identified the causative virus, TSPyV in the disease (van der Meijden et al., 2010). TSPyV viral loads average ~10^6 copies per cell in lesional skin samples compared to <10^2 copies per cell in non-lesional and healthy control skin samples (Kazem, 2012).

Children are often born with maternal antibodies to TSPyV, but begin producing their own antibodies in the first year after primary exposure (Chen et al., 2011; Fukumoto et al., 2015; van der Meijden et al., 2013). Transmission may occur through family members, possibly through respiratory secretions (Bialasiewicz et al., 2017; Pedergnana et al., 2017). Adult seroprevalence ranges from 63.2% to 81% (Chen et al., 2011; Nicol et al., 2013; Sroller et al., 2016; van der Meijden et al., 2011, 2013). Skin infection appears to be transient, as skin swabs show low prevalence of viral DNA (0–3.8% in adults) (Hampras et al., 2015; Schowalter et al., 2010; Wieland et al., 2014).

TS patients have numerous, mildly pruritic, folliculocentric, flesh-colored to pink papules with central keratinaceous spines (Figure 1a) (Haycox et al., 1999; Matthews et al., 2011; Sperling et al., 2004; van der Meijden et al., 2010). Alopecia favoring the eyebrows and sometimes skin thickening creating a leonine facies, may occur concomitantly (van der Meijden et al., 2010). All cases have been associated with iatrogenic immunosuppressive medications, including cyclosporine, prednisone, mycophenolate, azathioprine, methotrexate, tacrolimus, and numerous chemotherapies (Aleissa et al., 2017; Matthews et al., 2011). There is recent evidence that TS may result from a primary infection rather than viral reactivation (Bialasiewicz et al., 2017; van der Meijden et al., 2017).

Histology reveals distended anagen hair follicles with diluted infundibula that are plugged with refractile, dystrophic material (Figure 1b) (Haycox et al., 1999; Matthews et al., 2011; Sperling et al., 2004; van der Meijden et al., 2010). Hair shafts are poorly formed or absent (Haycox et al., 1999; van der Meijden et al., 2010). An expanded inner root sheath epithelium contains enlarged cells with increased trichohyaline granules and increased apoptotic cells (Figure 1c) (Haycox et al., 1999; Leitenberger et al., 2015; Sperling et al., 2004).

In the skin, TSPyV infects the inner root sheath keratinocytes (Fischer et al., 2012; Rouanet et al., 2016; Wanat et al., 2012). The virus has also been identified in the blood, cerebrospinal fluid, respiratory tract, urinary tract, feces, cardiac tissue, and renal allografts, suggesting it may be a systemic infection (Fischer et al., 2012; Rockett et al., 2013; Tsuzuki et al., 2014; Urbano et al., 2016; van der Meijden et al., 2017). Despite its broad tissue distribution, TSPyV has not been linked to other diseases (Fava et al., 2016; Toptan et al., 2016).

Successful treatments for TS have only been reported for a handful of patients. Clearance with cautious reduction in immunosuppressive therapies has been reported (Coogle et al., 2017; van der Meijden et al., 2017). Topical antiviral medicines (e.g., cidofovir 1% or 3%) and physical measures (e.g., plucking and shaving) have been successful (Aleissa et al., 2017; Barton et al., 2017; Benoit et al., 2010; Campbell et al., 2006; Coogle et al., 2017; Leitenberger et al., 2015; Santesteban et al., 2015; van der Meijden et al., 2017; Wanat et al., 2012). Treatment with oral valganciclovir, acitretin, and leflunomide has also been reported (Aleissa et al., 2017; Kassar et al., 2017). There have been some reports of success using combinations of the aforementioned therapies, such as the reduction of
immunosuppression combined with topical or oral therapies (Googe et al., 2017; van der Meijden et al., 2017) and the combination oral acitretin and oral valganciclovir (Aleissa et al., 2017).

**HUMAN POLYOMAVIRUSES 6 AND 7**

Rolling-circle amplification of human skin swabs identified the closely related HPyV6 and HPyV7 from the skin of healthy volunteers (Schowalter et al., 2010). Like MCPyV, their detection in healthy volunteers suggested the ability of these viruses to be shed through latent or subclinical infections. While most newborns are seropositive (~80% for HPyV6, ~60% for HPyV7), seropositivity fell after the first 6 months of life, then rose with older cohorts, consistent with HPyV6/7 infection early in life for most individuals (Nicol et al., 2013; van der Meijden et al., 2013). Adult seroprevalences are 69–83% for HPyV6 and 35–66% for HPyV7 in populations throughout the world (Gossai et al., 2016b; Nicol et al., 2013; Schowalter et al., 2010; Sroller et al., 2016; van der Meijden et al., 2013). Examination of skin swabs revealed the presence of HPyV6 in 12–27.6% samples and HPyV7 2.1–13.4% (Hampras et al., 2015; Hashida et al., 2017; Schowalter et al., 2010; Wieland et al., 2014). Higher levels were detected in an HIV-positive population (39% for HPyV6 and 21% for HPyV7) (Wieland et al., 2014).

Persistence of viral DNA shedding over 6 months in the majority of individuals further support chronic skin infection and asymptomatic shedding in a portion of individuals infected with HPyV6 and HPyV7 (Hashida et al., 2017).

The constellation of clinical findings of HPyV6/7 infection have been referred to as “HPyV6- and HPyV7-associated pruritic and dyskeratotic dermatoses,” “human polyomavirus-7-associated rash and pruritus,” and “HPyV-associated hyperproliferative keratinopathy plus/minus pruritus” (Canavan et al., 2017; Ho et al., 2015; Nguyen et al., 2017; Smith et al., 2018). Cutaneous HPyV6 and HPyV7 infection manifests with pruritic, brown to gray, lichenified plaques involving the trunk and extremities (Figure 1c) (Canavan et al., 2017; Ho et al., 2015; Nguyen et al., 2017; Smith et al., 2018). With the exception of one case occurring in a patient immunosuppressed from HIV infection (Nguyen et al., 2017), published cases have been associated with cardiac and lung transplants (Canavan et al., 2017; Ho et al., 2015; Smith et al., 2018). Immunosuppressive medicines in these organ transplant recipients included prednisone, azathioprine, sirolimus, tacrolimus, everolimus, and mycophenolate (Canavan et al., 2017; Ho et al., 2015; Smith et al., 2018). Histopathology reveals epidermal papillomatosis, dyskeratotic keratinocytes in the epidermis, and irregular columns of parakeratosis, the latter referred to as “peacock plumage,” “columnar

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**Table 1. Genomic features of cutaneous polyomaviruses**

<table>
<thead>
<tr>
<th>Polyomavirus</th>
<th>Reference Genome</th>
<th>Size (bp)</th>
<th>LT (AA)</th>
<th>ST (AA)</th>
<th>MT (AA)</th>
<th>ALTO (AA)</th>
<th>VP1/2/3 (AA)</th>
<th>MicroRNA</th>
<th>Cell Receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCPyV</td>
<td>NC_010277.2</td>
<td>5,387</td>
<td>817</td>
<td>186</td>
<td>—</td>
<td>248/250</td>
<td>423/241/196</td>
<td>Present</td>
<td>Ganglioside GT1b/glycosaminoglycans</td>
</tr>
<tr>
<td>TSPyV</td>
<td>NC_014361.1</td>
<td>5,232</td>
<td>697</td>
<td>198</td>
<td>332</td>
<td>131</td>
<td>376/113/195</td>
<td>—</td>
<td>GM1/sialylactose</td>
</tr>
<tr>
<td>HPyV6</td>
<td>NC_14406.1</td>
<td>4,926</td>
<td>669</td>
<td>190</td>
<td>—</td>
<td>—</td>
<td>387/136/215</td>
<td>—</td>
<td>ND (non-ganglioside)</td>
</tr>
<tr>
<td>HPyV7</td>
<td>NC_14407.1</td>
<td>4,952</td>
<td>671</td>
<td>193</td>
<td>—</td>
<td>—</td>
<td>380/129/290</td>
<td>—</td>
<td>ND (non-ganglioside)</td>
</tr>
<tr>
<td>MWPyV (HPyV10)</td>
<td>NC_018102.1</td>
<td>4,927</td>
<td>668</td>
<td>199</td>
<td>—</td>
<td>—</td>
<td>404/311/201</td>
<td>—</td>
<td>ND</td>
</tr>
</tbody>
</table>

— indicates no evidence for presence.

Abbreviations: AA, amino acid; ALTO, alternative T open reading frame; HPyV, human polyomavirus; MCPyV, Merkel cell polyomavirus; MWPyV, Malawi polyomavirus; LT, large T antigen; MT, middle T antigen; ND, not determined; ST, small T antigen; TSPyV, trichodysplasia spinulosa polyomavirus.

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**Table 2. Locations of large T and small T motifs and ligands**

<table>
<thead>
<tr>
<th>Motif</th>
<th>Large T</th>
<th>Small T</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DNA</td>
<td>Zinc Finger</td>
</tr>
<tr>
<td></td>
<td>DnaJ</td>
<td>WXXWW</td>
</tr>
<tr>
<td></td>
<td>Hsc70</td>
<td>WB1</td>
</tr>
<tr>
<td></td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>93—97</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>94—98</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>91—95</td>
<td>98—102</td>
</tr>
</tbody>
</table>

Abbreviations: HPyV, human polyomavirus; LSD, large T antigen stabilization domain; MCPyV, Merkel cell polyomavirus; MWPyV, Malawi polyomavirus; NLS, nuclear localization sequence; OBD, origin binding domain.

1 Not verified experimentally.
2 Indirect binding to p53.
3 Direct binding to p53.
Table 3. Seroprevalence, skin prevalence, and disease associations of cutaneous polyomaviruses

<table>
<thead>
<tr>
<th>Polyomavirus</th>
<th>Seroprevalence in Adults</th>
<th>DNA Prevalence on Adult Skin</th>
<th>Disease Associations</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCPyV</td>
<td>60–96% (Gossai et al., 2016a; Martel-Janin et al., 2013; Nicol et al., 2013)</td>
<td>40–61.5% (Hampras et al., 2015; Schowalter et al., 2010)</td>
<td>Merkel cell carcinoma (Feng et al., 2008; Kasem et al., 2008; Moshibi et al., 2017), Chronic lymphocytic leukemia (Pantulu et al., 2010)</td>
</tr>
<tr>
<td>TSPyV</td>
<td>63–81% (Chen et al., 2011; Nicol et al., 2013; Sroller et al., 2016; van der Meijden et al., 2011)</td>
<td>0–3.8% (Hampras et al., 2015; Schowalter et al., 2010; Wieland et al., 2014)</td>
<td>Trichodysplasia spinulosa (Kazem et al., 2012; Kazem et al., 2014; Matthews et al., 2011; van der Meijden et al., 2010), Human papillomavirus 6 associated pruritic and dyskeratotic dermatitis (H6PD) (Nguyen et al., 2017), BRAF inhibitor-associated epithelial neoplasms (Schrama et al., 2014)</td>
</tr>
<tr>
<td>HPyV6</td>
<td>69–88% (Sroller et al., 2016)</td>
<td>12–27.6% (Hampras et al., 2015; Schowalter et al., 2010; Wieland et al., 2014)</td>
<td>Human papillomavirus 6 associated pruritic and dyskeratotic dermatitis (H6PD) (Nguyen et al., 2017), Human papillomavirus 7 associated pruritic and dyskeratotic dermatitis (H7PD) (Canavan et al., 2017; Ho et al., 2015; Nguyen et al., 2017; Smith et al., 2018), Human thymic epithelial tumors (Rennspiess et al., 2015)</td>
</tr>
<tr>
<td>HPyV7</td>
<td>35–66% (Sroller et al., 2016)</td>
<td>2.1–13.4% (Schowalter et al., 2010; Wieland et al., 2014)</td>
<td>None</td>
</tr>
<tr>
<td>MWPyV/HPyV10</td>
<td>42–99% (Gossai et al., 2016a; Nicol et al., 2014)</td>
<td>3.4–9.3% (Wieland et al., 2014)</td>
<td>None</td>
</tr>
</tbody>
</table>

Abbreviations: HPyV, human polyomavirus; MCPyV, Merkel cell polyomavirus; MWPyV, Malawi polyomavirus; TSPyV, trichodysplasia spinulosa polyomavirus.

dyskeratosis,” or “tiered parakeratosis with dyskeratosis” (Figure 1d) (Canavan et al., 2018; Champagne et al., 2015; Ho et al., 2015; Nguyen et al., 2015; Rennspiess et al., 2015). In the upper dermis, there may be sparse, perivascular, lymphocytic infiltrates (Ho et al., 2015; Pock and Stork, 2010). Viral T antigen and capsid proteins have been identified within keratinocytes, strongly suggesting that keratinocytes are the principal cell infected by HPyV7 in these dermatoses (Ho et al., 2015; Nguyen et al., 2017). Compared to healthy, control, skin samples, viral loads in lesional skin samples are several orders of magnitude higher (~1.44×10^6 copies/LINE repeat vs. ~3.11×10^3 copies/LINE repeat for HPyV6, ~2.90×10^3 copies/LINE repeat vs. ~1.43×10^3 copies/LINE repeat for HPyV7; 7.28–32.27×10^2 copies/cell vs. 0.4 copies/cell for HPyV7) (Nguyen et al., 2017; Ho et al., 2015). HPyV6 has been linked to keratoacanthomas, BRAF inhibitor–associated epithelial neoplasms, and Kimura disease (Beckervordersandforth et al., 2016; Rascovan et al., 2016; Schrama et al., 2014). However, other research has refuted the link between HPyV6/HPyV7 and other skin diseases, including both neoplastic and inflammatory skin diseases (Bergallo et al., 2018; Fava et al., 2016; Frquin et al., 2014; Haeggblom et al., 2017; Schrama et al., 2012; Scola et al., 2012).

Like MCPyV and TSPyV, HPyV6 and HPyV7 have also been identified in other tissues. HPyV6 has been detected in tonsillar tissue, cerebrospinal fluid, human bile, the respiratory tract, and feces, while HPyV7 has been noted in tonsillar tissue, human thymic epithelial tumors, urine, the respiratory tract, and feces (Chan et al., 2017; Delbue et al., 2015; Franzen et al., 2016; Rennspiess et al., 2015; Rockett et al., 2013; Salakova et al., 2016; Zheng et al., 2015). No link has been found between HPyV6/7 and internal malignancy (Toptan et al., 2016).

Treatments for infections linked to HPyV6 and HPyV7 remain anecdotal. Specifically, topical and intravenous cidofovir have been successful in isolated cases of HPyV7 infection, likely through its inhibition of viral replication (Canavan et al., 2017; Smith et al., 2018). There are contradictory reports on the benefit of acitretin: one patient had complete resolution of his eruption with acitretin and another patient had no response (Canavan et al., 2017; Smith et al., 2018). Of note, the patient with complete resolution received acitretin 25 mg twice daily, while the nonresponder patient received 25 mg once daily, leaving open the possibility that the dose and frequency of treatment may impact the efficacy. No reports have investigated the use of cidofovir or acitretin for HPyV6 infection.

MALAWI POLYOMVIRUS (HUMAN POLYOMAVIRUS 10)
MWPyV was discovered in the stool from a healthy child in Malawi after pyrosequencing of purified virus-like particles (Siebrasse et al., 2012). A nearly identical species, HPyV10, was independently identified through rolling-circle amplification of viromes prepared from condyloma on the buttok of a patient with warts, hypogammaglobulinemia, infections, and myelokathexis syndrome (Buck et al., 2012). Follow-up studies have confirmed the presence of MWPyV/HPyV10 in the stool of both healthy individuals and those with acute diarrheal illness (Yu et al., 2012). The seroprevalence of MWPyV/HPyV10 is very high with estimates of 42–99% in adults (Gossai et al., 2016a; Nicol et al., 2014). Skin swabs detected the virus in 3.4% of healthy individuals and 9.3% of HIV-infected men (Wieland et al., 2014) (Table 3). Although MWPyV/HPyV10 DNA is most frequently detected in stool, it is also present in the skin and respiratory samples from symptomatic children (Rockett et al., 2013). Given these findings, it remains unclear whether the bona fide tissue tropism of this virus is the skin or whether it represents a superficial contamination of the epidermis from another tissue source, like the gastrointestinal or respiratory tracts.
Figure 1. Clinical and histologic features of human polyomavirus infections. (a) In trichodysplasia spinulosa, patients present with folliculocentric, flesh-colored and pink papules with complete eyebrow alopecia. Though not seen here, keratinaceous spines may protrude from the center of the papules. (b) These hair follicles are dilated and filled with dystrophic material. The hair shaft is malformed. Enlarged cells with increased trichohyaline granules are present in the inner root sheath epithelium (left, scale bar = 500 μm). Expansion of the inner root sheath epithelium is frequently noted (right, scale bar = 200 μm). (c) HPyV6/7 associated pruritic and dyskeratotic dermatitis (H6PD/H7PD) presents as gray-brown, lichenified plaques on the trunk and extremities. These changes were visible on the trunk and upper extremities in this patient’s posterior deltoid (left) and back (right). Clinical images reproduced with permission from (Smith et al., 2018). (d) Histology shows epidermal papillomatosis and irregular columns of parakeratosis (left, scale bar = 100 μm). Dyskeratotic keratinocytes and irregular columns of parakeratosis are visible at higher magnification (right, scale bar = 50 μm). Histologic images courtesy of Peter Pavlidakey.
CONCLUSIONS
In contrast to the hundreds of species of papillomaviruses, there appears to be a smaller cohort of PyVs (n = 10–15) that infects humans. Seroprevalence studies have revealed that many of the more recently discovered PyVs appear to be zoonotic (Kamminga et al., 2018), perhaps suggesting that the discovery of HPyVs is nearing saturation. Five HPyVs are shed chronically from human skin at varying levels. Recent work has linked TSPyV to a folliculocentric eruption; HPyV6 and HPyV7 to diffuse, hyperproliferative, pruritic eruptions; and MCPyV to a deadly skin cancer. MWPyV has not yet been linked to any diseases. Despite similarities in their overall genomic structures, subtle differences in both the early and late regions of these cutaneous PyVs in concert with interactions with the host tissues allow the viruses to have distinct tissue tropism and clinical manifestations.

Serologic studies have revealed that cutaneous PyV infections occur in most individuals, yet even among immunosuppressed patients, PyV-mediated diseases are exceedingly rare. Additional studies are necessary to identify the PyV- and host-specific factors that drive the development of clinically relevant infections in rare individuals. Hopefully, these studies will also yield better treatments for the patients who develop these rare, but serious infections. Additional studies may reveal whether cutaneous PyVs contribute to currently idiopathic inflammatory skin conditions or exacerbate common skin diseases. These studies may also reveal whether cutaneous PyVs play commensal or even beneficial roles as members of the skin microbiome. Finally, consistent with the groundbreaking studies of SV40, the continued study of cutaneous PyVs will likely continue to contribute to our understanding of human tumorigenesis.

CONFLICTS OF INTEREST
The authors state no conflict of interest.

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polyomavirus small T antigen controls viral replication and oncoprotein 
Leitenberger JJ, Abdelmalek M, Wang RC, Strasfeld L, Hopkins RS. Two cases of 
trichodysplasia spinulosa responsive to compounded topical cidofovir 
Martel-Jantin C, Pedernegana V, Nicol JT, Leblond V, Tregouet P, et al. Merkel cell polyomavirus infection occurs during early childhood and 
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