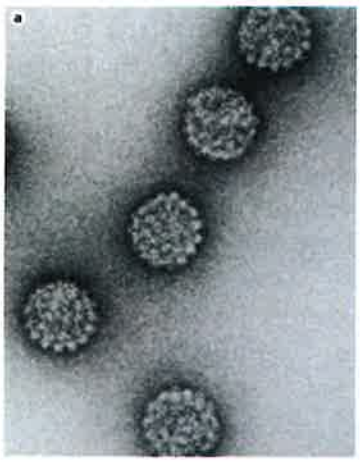
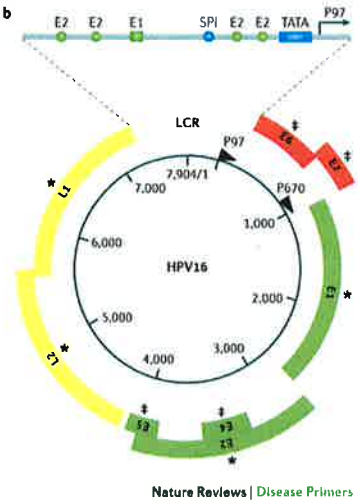
DR. R. PICKLES 2018

Human Papilloma Virus (HPV)

Family: Papillomaviridae **Genus:** *Papillomavirus*

Small non-enveloped double-stranded DNA virus, encased in 72-sided icosahedral protein capsid. HPV genome consists of circular double-stranded DNA approx. 7900 base pairs. Virions contain at least 2 capsid proteins, major capsid protein 56 kd, minor capsid protein mw 76 kd.





HPV genome is divided functionally into 3 regions: 1) Transcription and replication control 2) early region encoding proteins for replication, regulation and modification of host cytoplasm and nucleus, and 3) late region encoding capsid proteins
Non-coding upstream regulatory region controlling DNA replication and transcription of 8-9 open reading frames (ORFs) divided into early (E1-7) and late (L1-2) regions.
E1 involved in viral replication, E2 modulates viral transcription; E4 proteins form filamentous cytoplasmic networks; E5 stimulates transforming activity of epidermal growth factor and contributes to oncogenicity; E6 binds to p53 tumour suppressor gene

HPVs belong to 5 genera of the 38 in the Paillomaviridae family, alpha, beta, gamma, mu, nu. Genus further divided into species; eg alphapapillomavirus HPV-16 is representative of species 9, which also includes types 31, 33, 35, 52 + 67; >184 HPV types characterised; distinct types share <90% base pair homology with other types.
HPVs are host-specific, and each type largely associated with distinct histopathologic process.

Epidemiology

Incidence and prevalence – subclinical and latent infection common; common and plantar warts (HPV 1,2,4) seen in up to 20% of school age children; prior to immunisation, most sexually active adults infected over a lifetime (HPV 6,11,16,18).
Transmission – close physical contact; genital warts in children can occur after hand contact with non-genital lesions; recurrent respiratory papillomatosis thought to be acquired via passage through birth canal; transmission through fomites and nosocomial transmission documented (infectious virus found in fumes of CO_2 laser or electrocoagulation).

Association with malignancy

Long established role in genital tract malignancy - high risk oncogenic types including 16, 18, 31, 33 with ORs of 100-900 in cervical SCC and adenocarcinomas; strong role in vulval, vaginal, penile and anal SCC; increasing role in oropharyngeal cancers.

Pathogenesis

Incubation period 6 weeks – 2 years in experimental common wart infection (commonly warts appear after 3-4 months); all types of squamous epithelium may be infected, but other tissues, except cervical glandular epithelium, appear resistant.
Virus replication depends on epithelial differentiation, beginning with entry into stratum basale via breach in epithelial integrity; as basal cells differentiate and progress to epithelial surface, HPV DNA replicates and is transcribed and viral particles are assembled in cell nucleus. Complete virions are released. Viral replication is associated with excessive proliferation of all epithelial layers except basal layer, producing acanthosis, parakeratosis, and hyperkeratosis; some cells undergo characteristic vacuolation termed koilocytosis; excessive basal-like cell proliferation with high nuclear/cytoplasmic ratio with high number of mitoses is feature of incipient and malignant HPV disease. Presence of residual HPV DNA after treatment of warts associated with recurrent disease.

Integration into host DNA disrupts E2 ORF which plays a role in pathogenesis of malignant disease. HPV E 5, 6 and 7 proteins suppress the host immune system at various levels allowing persistence and progression of HPV infection.
Host immune responses poorly understood, however immune deficient states result in persistent warts and malignant transformation.

Clinical manifestations

Cutaneous – deep plantar, common and plane or flat warts
Epidermodysplasia verruciformis – autosomal recessive genodermatosis linked to gene loci on chromosome 17, involving many HPV types
Anogenital warts – wide range of lesions including urethral, subpreputial, penile shaft, scrotal and perianal lesions in men; posterior introitus, labia majora, minora, and clitoris most common in women; types 6 + 11 mostly associated with benign condylomata, with types 16+18 associated with intraepithelial neoplasia. 75% with anogenital warts are asymptomatic, with others experiencing itching, burning, and pain as well as significant psychological effects; spontaneous clinical remission occurs in 10-20% over 3-4 months.
Recurrent respiratory papillomatosis – seen in infancy and childhood, may result in rapid spread down tracheobronchial tree; adult form less aggressive, although malignant transformation may occur.
Orai squamous papillomas, orai verrucae vulgaris also seen in oral cavity
Diagnosis mostly clinical; biopsy if doubt or malignancy suspected; cervical cytology and HPV DNA testing.

Treatment

No curative treatment exists – all therapies largely cosmetic/symptomatic recognising that spontaneous clearance does occur in some patients.
Chemical therapies or immunomodulatory: **cutaneous warts** – salicylic acid, cryotherapy (liquid nitrogen or CO_2), imiquimod (immunomodulator inducing IFN + other cytokine production), laser/electrocautery.
Anogenital warts – patient-applied therapies increasingly utilised; podophyllotoxin (derivative of *podophyllum peltatum* or *emodi* rhizome), imiquimod, cryotherapy, and surgical methods; TCA less often used; intralesional interferon or cidofovir described but expensive and no more effective.

Prevention

Avoidance of contact the only sure way of preventing cutaneous warts; consistent condom use shown to reduce male and female acquisition of genital warts/HPV acquisition and promotes regression of HPV-associated cervical and penile lesions;
Pap smear increasingly supplanted by direct HPV testing; anal cytology screening in HIV infection controversial.
Vaccination with Cervarix (HPV 16,18) and Gardasil (6,11,16,18) have both been shown to be highly efficacious in preventing infection with these serotypes – production of non-infectious HPV L1 VLPs by bakers yeast, inducing neutralising antibodies; covers 70% ca cx causing strains. Gardasil 9 (6,11, 16,18,31,33,45,52,58) latest addition with 9 serotypes, increases ca cx coverage to 90%. Gardasil vaccination in Australia -> 93% reduction genital warts in women <21 yrs with similar effects on CIN. Gardasil now offered free to HIV positive men up to 35 years in NSW.

Women <26yr rec for Imm^n

Vaccine may have therapeutic effect.

TCA
trichloracetic acid