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RECOMMENDATION

E5, the third oncogene of Papillomavirus

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Based on reviews by:

Leonardo de Oliveira Martins and one anonymous reviewer

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A recommendation of

Willemsen A, Féllez-Sánchez M, and Bravo IG. Genome plasticity in Papillomaviruses and *de novo* emergence of *E5* oncogenes. *bioRxiv* 337477, ver 3 peer-reviewed and recommended by *PCI Evol Biol* (2019). doi: 10.1101/337477

Papillomaviruses (PVs) infect almost all mammals and possibly amniotes and bony fishes. While most of them have no significant effects on the hosts, some induce physical lesions. Phylogeny of PVs consists of a few crown groups [1], among which AlphaPVs that infect primates including human have been well studied. They are associated to largely different clinical manifestations: non-oncogenic PVs causing anogenital warts, oncogenic and non-oncogenic PVs causing mucosal lesions, and non-oncogenic PVs causing cutaneous warts.

The PV genome consists of a double stranded circular DNA genome, roughly organized into three parts: an early region coding for six open reading frames (ORFs: E1, E2, E4, E5, E6 and E7) involved in multiple functions including viral replication and cell transformation; a late region coding for structural proteins (L1 and L2); and a non-coding regulatory region (URR) that contains the cis-elements necessary for replication and transcription of the viral genome.

The *E5*, *E6*, and *E7* are known to act as oncogenes. The E6 protein binds to the cellular p53 protein [8]. The E7 protein binds to the retinoblastoma tumor suppressor gene product, pRB [2]. However, the *E5* has been poorly studied, even though a high correlation between the type of E5 protein and the infection phenotype is observed. *E5s*, being present on the E2/L2 intergenic region in the genomes of a few polyphyletic PV lineages, are so diverged and can only be characterized by high hydrophobicity. No similar sequences have been found in the sequence database.

Féllez-Sánchez *et al.* [3] provide valuable evidence on the origin and evolutionary history



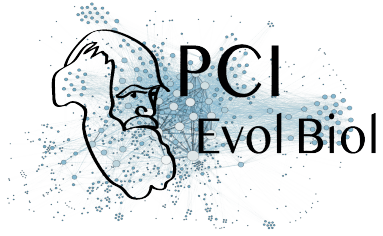
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of E5 genes and their genomic environments. First, they tested common ancestry vs independent origins [7]. Because alignment can lead to biased testing toward the hypothesis of common ancestry [9], they took full account of alignment uncertainty [6] and conducted random permutation test [5]. Although the strong chemical similarity hampered decisive conclusion on the test, they could confirm that E5 may do code proteins, and have unique evolutionary history with far different topology from the neighboring genes.

Still, there is mysteries with the origin and evolution of *E5* genes. One of the largest interest may be the evolution of hydrophobicity, because it may be the main cause of variable infection phenotype. The inference has some similarity in nature with the inference of evolutionary history of G+C contents in bacterial genomes [4]. The inference may take account of possible opportunity of convergent or parallel evolution by setting an anchor to the topologies of neighboring genes.

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Appendix

Reviews by Leonardo de Oliveira Martins and one anonymous reviewer, DOI:
10.24072/pci.evolbiol.100067