Comprehensive comparison of the interaction of the E2 master regulator with its cognate target DNA sites in 73 human papillomavirus types by sequence statistics.

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Mucosal human papillomaviruses (HPVs) are etiological agents of oral, anal and genital cancer. Properties of high- and low-risk HPV types cannot be reduced to discrete molecular traits. The E2 protein regulates viral replication and transcription through a finely tuned interaction with four sites at the upstream regulatory region of the genome. A computational study of the E2-DNA interaction in all 73 types within the alpha papillomavirus genus, including all known mucosal types, indicates that E2 proteins have similar DNA discrimination properties. Differences in E2-DNA interaction among HPV types lie mostly in the target DNA sequence, as opposed to the amino acid sequence of the conserved DNA-binding alpha helix of E2. Sequence logos of natural and in vitro selected sites show an asymmetric pattern of conservation arising from indirect readout, and reveal evolutionary pressure for a putative methylation site. Based on DNA sequences only, we could predict differences in binding energies with a standard deviation of 0.64 kcal/mol. These energies cluster into six discrete affinity hierarchies and uncovered a fifth E2-binding site in the genome of six HPV types. Finally, certain distances between sites, affinity hierarchies and their eventual changes upon methylation, are statistically associated with high-risk types.

Keywords: Protein-DNA interaction, Berg–von Hippel theory, human papillomaviruses
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