

Distinct human papillomavirus type 16 methylomes in cervical cells at different stages of premalignancy. ^[1]

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Abstract

Human papillomavirus (HPV) gene expression is dramatically altered during cervical carcinogenesis. Because dysregulated genes frequently show abnormal patterns of DNA methylation, we hypothesized that comprehensive mapping of the HPV methylomes in cervical samples at different stages of progression would reveal patterns of clinical significance. To test this hypothesis, thirteen HPV16-positive samples were obtained from women undergoing routine cervical cancer screening. Complete methylation data were obtained for 98.7% of the HPV16 CpGs in all samples by bisulfite-sequencing. Most HPV16 CpGs were unmethylated or methylated in only one sample. The other CpGs were methylated at levels ranging from 11% to 100% of the HPV16 copies per sample. The results showed three major patterns and two variants of one pattern. The patterns showed minimal or no methylation (A), low level methylation in the E1 and E6 genes (B), and high level methylation at many CpGs in the E5/L2/L1 region (C). Generally, pattern A was associated with negative cytology, pattern B with low-grade lesions, and pattern C with high-grade lesions. The severity of the cervical lesions was then ranked by the HPV16 DNA methylation patterns and, independently, by the pathologic diagnoses. Statistical analysis of the two rating methods showed highly significant agreement. In conclusion, analysis of the HPV16 DNA methylomes in clinical samples of cervical cells led to the identification of distinct methylation patterns which, after validation in larger studies, could have potential utility as biomarkers of neoplastic cervical progression.

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