Human papillomavirus (HPV) is a significant risk factor for cervical cancer and various other malignancies. The ~8 kb viral genome is divided into three regions: early, late, and long control region (LCR). We focused on the early region, encoding E1, E2, E6, and E7 proteins crucial for viral replication, transcription, and oncogenesis.

To understand the evolutionary conservation of these proteins, we conducted an in-depth analysis of invariant residues across different HPV species. We used already categorized HPV types (Categorized by a >10% change in the L1 major capsid protein) Alpha, Beta, and Gamma papillomaviruses. Our analysis revealed distinct patterns of conservation within each group and across the entire HPV family.

**Alpha papillomaviruses** exhibited 132 invariant residues in E1, 52 in E2, 22 in E6, and 10 in E7. **Beta papillomaviruses** showed higher conservation with 191, 108, 38, and 22 invariant residues, respectively. **Gamma papillomaviruses** displayed 107, 60, 20, and 16 invariant residues in these proteins. When considering all three species together, conservation decreased significantly to 98, 41, 15, and 7 invariant residues for E1, E2, E6, and E7, respectively. The E2 binding sites within the LCR were compiled and classified into high-risk, low-risk, and probable high-risk strains using the 12 nucleotide palindromic DNA sequences of the four E2 binding sites.

These findings suggest that while some residues are crucial for overall HPV function, specific adaptations have occurred within each species. Identifying these invariant residues provides valuable insights into protein structure, function, and potential targets for therapeutic interventions. Further research is needed to elucidate the functional significance of these conserved residues.