Low-risk type human papillomavirus (HPV) 6 and 11 infection causes recurrent respiratory papillomatosis (RRP) and genital warts. RRP is the most common benign tumor of the larynx in children with frequent relapses. Repeated surgeries are often needed to improve vocal function and prevent life-threatening respiratory obstruction. Currently, there are no effective treatments available to completely eliminate these diseases, largely due to limited knowledge regarding their viral molecular pathogenesis. HPV E6 proteins contribute to cell immortalization by interacting with a variety of cellular proteins, which have been well studied for the high-risk type HPVs related to cancer progression. However, the functions of low-risk HPV E6 proteins are largely unknown. In this study, we report GST-pulldown coupled mass spectrometry analysis with low-risk HPV E6 proteins that identified sterile alpha motif domain containing 9 (SAMD9) as a novel interacting partner. We then confirmed the interaction between HPV-E6 and SAMD9 using co-immunoprecipitation, proximity ligation assay, and confocal immunofluorescence staining. The SAMD9 gene is down-regulated in a variety of neoplasms and deleteriously mutated in normophosphatemic familial tumoral calcinosis. Interestingly, SAMD9 also has antiviral functions against poxvirus. Our study adds to the limited knowledge of the molecular properties of low-risk HPVs and describes new potential functions for the low-risk HPV E6 protein.