Helicobacter pylori, a gram-negative bacterium that colonizes the human gastric mucosa, is recognized as a major risk factor for gastric diseases, such as peptic ulcer and gastric cancer. H. pylori delivers an effector protein CagA into gastric epithelial cells. The CagA is localized to the inner surface of the plasma membrane and an EPIYA segment in the C-terminal intrinsically disordered region of CagA is phosphorylated by the Src kinase. The phosphorylated EPIYA segment (EPIpYA segment) then interacts with the tandem SH2 domain of a cellular signaling molecule SHP2 (SH2_SHP2) to deregulate the phosphatase activity of SHP2, causing aberrant activation of pro-oncogenic Erk MAP kinase signaling. It has been widely known that CagA derived from East Asian type H. pylori is more pathogenic than Western one, and there are some primary structure differences in the EPIYA segment between them. To understand the molecular mechanism of the different pathogenicity between Western and East Asian CagA, we have analyzed the EPIpYA-SH2_SHP2 interaction using SPR and determined the crystal structures of EPIpYA-SH2_SHP2 complexes with Western and East Asian types of the EPIpYA segments. The SPR analysis revealed that the East Asian EPIpYA segment showed significantly higher affinity for SH2_SHP2 than that of Western one. The crystal structures identified critical residues for the high affinity binding in the East Asian EPIpYA segment. Biochemical and small angle X-ray scattering analyses suggested that the EPIpYA-SHP2 complex formation proceeds via a two-step mechanism. In addition, Western and East Asian CagA molecules seem to utilize distinct strategies for the stable CagA-SHP2 complex formation. Our two-step model of the CagA-SHP2 interaction well explains mechanisms of disease related mutations found in SHP2.