Rheumatoid arthritis (RA) is a chronic systemic autoimmune disorder of unknown etiology, which is characterized by inflammation in the synovium and joint damage. Although the pathogenesis of RA remains to be determined, a combination of environmental (e.g., viral infections) and genetic factors influence disease onset. Especially genetic factors play a vital role in the onset of disease, as the heritability of RA is 50–60%, with the human leukocyte antigen (HLA) alleles accounting for at least 30% of the overall genetic risk. Some HLA-DR alleles encode a conserved sequence of amino acids, referred to as the shared epitope (SE) structure. By analyzing the structure of a HLA-DR molecule in complex with Epstein-Barr virus (EBV), the SE motif is suggested to play a vital role in the interaction of MHC II with the viral glycoprotein (gp) 42, an essential entry factor for EBV. EBV has been repeatedly linked to RA by several lines of evidence and, based on several findings, we suggest that EBV is able to induce the onset of RA in predisposed SE-positive individuals, by promoting entry of B-cells through direct contact between SE and gp42 in the entry complex.