HLA-DRB1*04 as a risk allele to systemic Lupus Erythematosus and Lupus Nephritis in the Malay population of Malaysia

ABSTRACT

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease afflicting multiple organs. Lupus nephritis (LN) is a serious complication of SLE and remains a major cause of mortality and morbidity. Curative therapy remains unavailable as etiology from genetic and environmental factors is still unclear. The present study was conducted to elucidate the link between HLA-DRB1 gene polymorphisms with SLE and LN through clinical and laboratory/biological presentations in a population of Malaysian Malay females with SLE. A total of 100 Malay female SLE patients inclusive of 70 SLE patients without LN and 30 patients with LN were included in this study. HLA-DRB1 allele examination in SLE patients was performed using PCR-SSO, and the alleles' frequencies were compared with 951 publicly available datasets representing Malay healthy controls in Malaysia. Cytokines and free radical levels were detected by ELISA and bead-based multiplexed Luminex assays. The association between HLA-DRB1 alleles with clinical and serological manifestations and immune mediators was analyzed using different statistical approaches whenever applicable. Our study showed that HLA-DRB1*0405, HLA-DRB1*1502, and HLA-DRB1*1602 were associated with the increased risk of SLE while HLA-DRB1*1201 and HLADRB1*1202 alleles were associated with a lower risk of SLE development. Furthermore, HLA-DRB1*04 showed significant association to LN and arthritis while HLA-DRB1*15 was significantly associated with oral ulcer in Malay SLE patients. Association analysis of HLA-DRB1*04 with clinical and biological factors revealed that HLA-DRB1*04 was significantly associated with Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) scores, anti-nuclear antibody (ANA), C-reactive protein (CRP) in the blood, and total protein in the urine. SLE carriers with the HLA-DRB1*04 allele were significantly correlated to the increased levels of cytokines (IFN-y, GM-CSF, IL-17F, IL-18, IL-21, and VEGF) and were significantly showing negative correlation to IL-5 and free radicals (LPO and catalase enzyme) levels compared to SLE carriers without HLA-DRB1*04 allele. The results suggested that disease severity in SLE may be determined by HLA-DRB1 alleles. The risk of HLA-DRB1*04 allele with LN was supported by the demonstration of an intense inflammatory response in Malay SLE patients in Malaysia. More studies inclusive of a larger and multiple SLE cohorts in the future are warranted to validate these findings.

Keyword: Systemic lupus erythematosus; Lupus nephritis; HLA-DRB1 gene polymorphism; HLA-DRB1∗04; Malaysian Malay population; Cytokines and free radicals