CONCISE REPORT

TAP1 and TAP2 polymorphisms analysis in northwestern Colombian patients with systemic lupus erythematosus

P A Correa, J F Molina, L F Pinto, M Arcos-Burgos, M Herrera, J-M Anaya


Objective: To determine the influence of TAP1 and TAP2 alleles in northwestern Colombian patients with systemic lupus erythematosus (SLE).

Methods: Unselected patients with SLE (n=140) and controls (n=120) matched for sex, age, and ethnicity were analysed. Clinical manifestations, clinical activity, and severity of disease were recorded. Autoantibodies were detected by enzyme linked immunosorbent assay (ELISA). TAP1 and TAP2 polymorphisms were determined by amplification refractory mutation system-polymerase chain reaction. A Hardy-Weinberg equilibrium test, microdifferen-
tiation analysis, linkage disequilibrium analysis, and haplotype and allele frequency comparisons were performed.

Results: The TAP2 variant Val379/Ala565/Ala665 (allele TAP2*0201) was associated with SLE (56% v 39%; odds ratio=2, 95% confidence interval 1.22 to 3.30, p=0.03). There was no stratification between patient and control samples. Linkage disequilibrium between TAP1 and TAP2 loci was found in controls but not in patients. An excess in the number of heterozygotes in the TAP2 locus was found in patients. No association between TAP1 and TAP2 variants and the presence of autoantibodies, clinical expression, or severity of disease was found.

Conclusions: The TAP2 locus influences susceptibility to SLE in our patient group; however, it has no significant effect on the immune response or on the clinical course of the disease.

Systemic lupus erythematosus (SLE) is a clinically heterogeneous autoimmune disease of unknown aetiology, in which environmental, genetic, and ethnic factors may have an important role. The human leucocyte antigen (HLA) HLA-DR2 and DR3 alleles have been associated with SLE in numerous studies, mainly with the production of anti-Ro and anti-La autoantibodies. Other susceptibility candidate genes may include tumour necrosis factor α, mannose binding protein, interleukin 10, angiotensin converting enzyme, and deficiencies of components of the complement system.

Transports associated with antigen processing (TAP) genes (TAP1 and TAP2) may also be considered as a susceptibility factor for SLE. TAP1 and TAP2 are polymorphic genes located in the class II region of the major histocompatibility complex (MHC) between HLA-DP and HLA-DQ genes. TAP genes code for a homologous molecule to the ATP binding cassette (ABC) transporters that conforms to the chaperons ABC superfamily. TAP is a dimer responsible for transportation of antigenic peptides bound to HLA class I, but the contribution of TAP molecules to endogenous processing of peptides bound to HLA class II has also been reported.

Four potential alleles for the TAP1 gene and eight alleles for the TAP2 gene have been reported with some single nucleotide polymorphism in each gene. TAP genes are interesting candidates for the study of genetic susceptibility in autoimmune diseases given their location at the MHC class II region, their functional relation with HLA molecules, and their polymorphism.

A few studies have evaluated the association of TAP1 and TAP2 with SLE. In the Latin-American population no information exists about these genes and SLE. Thus, we examined the influence of TAP1 and TAP2 polymorphisms on the susceptibility, clinical expression, and severity of SLE, as well as on the production of autoantibodies in northwestern Colombian patients.

Patients and Methods

Study group

This was a multicentre, cross sectional study. The patients with SLE were recruited in Medellín, Colombia. All patients fulfilled four or more of the American College of Rheumatology (ACR) criteria for the classification of SLE. Healthy people unrelated to the patients, without inflammatory or autoimmune disease, matched to patients by age (±5 years), sex, and ethnicity were included as controls. This study had the approval of the local ethics committee.

Clinical and laboratory features

The clinical and laboratory variables associated with SLE, including each feature of the revised ACR criteria, were evaluated. These clinical manifestations were defined as follows: (a) arthritis: non-erosive arthritis affecting two or more peripheral joints, characterised by tenderness, swelling, or effusion; (b) malar rash; (c) photosensitivity; (d) alopecia; (e) discoid lupus; (f) Raynaud’s phenomenon; (g) renal disease, as evidenced by a renal biopsy result demonstrating World Health Organisation (WHO) class II–V histopathology, active urinary sediment, or proteinuria >500 mg/24 h; (h) neurological disease, as evidenced by seizures without any other definable cause, or psychosis lacking any other definable cause, or other conditions such as peripheral neuropathy, stroke, transverse myelitis, chorea, or other central nervous system lesions directly attributable to SLE in the absence of other causes; (i) pleuritis: pleural rub and/or effusion and/or typical pleuritic pain; (j) pericarditis: documented by electrocardiogram, rub, or evidence of pericardial effusion; (k) autoimmune haemolytic anaemia, with a packed cell volume of <0.33, reticulocyte count >4%, and positive Coombs test; (l) leucopenia, white cells <4.0×10⁹/l; (m) thrombocytopenia, platelets <100×10⁹/l; (n) arterial or venous thrombosis diagnosed on clinical grounds and confirmed by complementary tests.

The severity of the disease and the organic damage, was evaluated using the systemic lupus international collaborating clinics (SLICC) damage index (SDI).

Abbreviations: ACR, American College of Rheumatology; CI, confidence interval; MHC, major histocompatibility complex; OR, odds ratio; SLE, systemic lupus erythematosus
TAP1 and TAP2 genotyping

TAP1 and TAP2 polymorphisms were identified by amplification refraction mutation system-polymerase chain reaction, using primers and conditions described elsewhere. Each of the alternatives was typical for the diallelic sites corresponding to amino acid positions 333 and 637 in TAP1 and positions 379, 565, and 665 in TAP2.

Statistical and genetic data analysis

We examined the possibility of subdivision among patients and controls, the Hardy-Weinberg equilibrium, and linkage disequilibrium among loci as described elsewhere. Differences between the patient and control marker gene frequencies were established by \( \chi^2 \) test. Crude odds ratios (OR) were estimated and reported with its corresponding 95% confidence interval (CI). The Bonferroni correction for multiple comparisons was applied. A level of 5% was used to define statistical significance.

RESULTS

One hundred and forty patients with SLE and 120 controls were included in the study. Table 1 shows the clinical and serological characteristics of patients. In patients and controls the combination Ile333/Asp637 in TAP1 and Val379/Ala565/Thr665 in TAP2 were the most frequently found (table 2).

We found a significant difference in the frequencies of the single nucleotide polymorphisms among patients and controls for TAP2, but not for TAP1. The variant Val379/Ala565/Ala665 in TAP2 was found more often in patients than in controls (56% v 39%, OR=2, 95% CI 1.22 to 3.30, p=0.005). There were nine control homozygates for TAP2, but none of the patients was homozygous for this combination (OR=0.7, 95% CI 0.2 to 2.4, p=0.7). However, no effect of gene dose on susceptibility to disease was observed.

The haplotype frequencies among the TAP1-TAP2 interloci combination were estimated. The most common haplotypes in patients and controls were TAP1 Ile333/Asp637-TAP2 Val379/Ala565/Thr665 (39% and 36% respectively). Associations between TAP1 and TAP2 variants and the presence of autoantibodies, clinical parameters, or the severity of disease were not observed.

DISCUSSION

Our results provided genetic evidence indicating that the TAP2 locus influences the susceptibility to SLE in our population. Firstly, an allelic misbalance in TAP2 was clearly seen between patients and controls. The TAP2 Val379/Ala565/Ala665 variant was associated with SLE. It is noteworthy that stratification among patients and controls was not found. Secondly, there was greater genetic selection in the TAP2 locus in patients because there was an excess in the number of heterozygotes. Thirdly, no linkage disequilibrium was observed between TAP1 and TAP2 loci in patients, suggesting a high mutation rate at the TAP2 locus in this study. The analysis also disclosed that TAP variants have no significant influence on the immune response or the course of the disease.

The frequencies of TAP1 and TAP2 variants found in controls were similar to those observed in white, Brazilian, and African populations. This result suggests that from an evolutionary point of view TAP genes are relatively ancient. TAP molecules have an essential role in antigen processing and presentation to cytotoxic T lymphocytes. The TAP heterodimer is composed of TAP1 and TAP2 subunits which may function together or independently as homodimers, transporting antigenic peptides from the cytoplasm into the lumen of the endoplasmic reticulum. The association of the TAP2 molecule with the selected peptide may depend on specific positions inside such peptide(s), which will link to posi-...
In the patients we found no linkage disequilibrium between TAP1 and TAP2. However, a further study on HLA polymorphism should elucidate whether or not TAP alleles are in linkage disequilibrium with HLA in our population.

In summary, the TAP2 locus influences the susceptibility to SLE in a northwestern Colombian population; however, it has no effect on the immune response or on the clinical expression of the disease.

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