akayasu arteritis (TA) is a chronic vasculitis of unknown etiology that involves the aorta and its main branches, such as the innominate, carotid, subclavian, vertebral, and renal arteries, as well as the pulmonary and coronary arteries. This disease is more common in young females in Asia, Middle East, and Middle and South America than in Europe and North America. TA has 2 stages: an acute, “pre-pulseless” phase characterized by non-specific inflammation of the large vessels, followed by a chronic, “pulseless” phase with thickening of the whole vascular wall and sequent luminal narrowing. The histological feature of acute-phase TA is a panarteritis extending from the adventitia to the media: the adventitia shows massive infiltration of T cells (CD4+ T cells, CD8+ T cells, γδ T cells, and natural killer cells), neutrophils, macrophages, and dendritic cells. The media is characterized by infiltration of T cells and giant cells and rich neovascularization. In the chronic phase, the thickening of the entire vascular wall is accompanied by adventitial fibrosis, medial fragmentation (because of the destruction of elastic fibers), and intimal thickening associated with proliferation of smooth muscle cells and myofibroblasts and deposition of the extracellular matrix, which leads to luminal narrowing and vascular occlusion.

A role of some genetic factors is suggested in the pathogenesis of TA, because the disease prevalence shows ethnic differences and genetically identical twin cases have been reported. Thus, human leukocyte antigen (HLA) in TA patients was studied with great enthusiasm in the 1980s–1990s. TA has been associated with different HLA alleles in different populations (Table): in Japan, the incidence of HLA-B52 and B39 alleles, as well as other haplotypes, are increased in TA patients compared with normal subjects. Increased expressions of HLA-DRB1*07 allele and HLA-DBR1*09 and DBR1*1701 alleles were shown in TA patients in Korean and Chinese Han populations, respectively. Susceptibility to TA has been associated with HLA-B5, B21, and DR8 alleles in India, HLA-B39, B15, B40, and DR6 alleles in Mexico, and HLA-DR10 and DR16 alleles in Colombia. It is noteworthy that differential allele expression has been correlated with a variation in clinical symptoms. HLA-B52 is considered a conventional risk allele for TA, HLA-B52-positive TA patients have more severe inflammation, a higher incidence of coronary artery involvement, and a worse prognosis. More steroids are needed to control the activity in HLA-B52-positive patients. Aortic regurgitation, pulmonary infarction, and coronary artery disease are frequently found in HLA-B52-positive/B39-negative TA patients, whereas HLA-B39-positive patients have more renal artery involvement.

In this issue of the Journal, Takamura et al report a new locus, HLA-B67, associated with TA in a Japanese population. Although the prevalence of the HLA-B67 allele was lower than that of B52, the conventional risk allele, the odds ratio of the B67 allele was higher than that of B52. The distribution of affected arteries, the incidence of complications (ie, hypertension and aortic regurgitation), and the response to treatment, such as the incidence of steroid resistance and recurrent cases, were similar in HLA-B67-positive TA patients and HLA-B52-positive patients (Figure). Interestingly, the HLA-B67 allele is a specific HLA genotype for East Asia, but not reported in Caucasians or Africans, suggesting that the HLA-B67 allele would be new risk allele of TA specific for Asians.

From the viewpoint of the molecular mechanism of TA, a possible role of a specific epitope (63Glu and 67Ser) located on the peptide-binding site of the HLA B molecule has been underscored, because HLA-B52 and B39 alleles share the epitope. The shared residues are suggested to participate in the presentation of a limited number of antigen-derived peptides to the CD4+ T cells, the major infiltrating cells in the arterial wall of TA patients. It is interesting to know whether HLA-B67 allele shares the specific epitope. HLA-B52 positive TA patients have been considered to have a severer clinical manifestation than HLA-B52 negative patients. However, Takamura et al report no apparent differences in the clinical characteristics of HLA-B52-positive and HLA-B52-negative patients.
-negative patients in their cohort. The discrepancy between this present study and previous studies may be explained by the improved prognosis of TA patients over the past decade. Recent developments in noninvasive diagnostic imaging modalities, such as the high-resolution ultrasonography, multidetector-row computed tomography, magnetic resonance imaging, and positron-emission tomography, and the improvement in medical treatments using steroids and immunosuppressive agents offer the best option for early and correct diagnosis and monitoring of disease activity and response to treatment, which may obscure differences in the clinical findings and severity between TA patients with and without high-risk HLA alleles. To determine the clinical features and prognosis of HLA-B67-positive TA patients, we await accumulation of a large number of patients with this HLA allele.

References