41 Genetics of Antiphospholipid Syndrome

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Introduction

The phenotypes of autoimmune diseases are related with both genetic and environmental factors. The antigen specificity of antiphospholipid antibodies (aPL) and the pathophysiology of thrombosis in antiphospholipid syndrome (APS) are highly heterogeneous and multifactorial, thus a single scenario cannot explain the mechanisms of thrombophilia or pregnancy morbidity present in affected patients.

A genetic predisposition for developing diseases is supported by various facts, such as concordance of disease in identical twins and in patients' relatives, increased frequency in certain ethnic groups, and elevated frequency of some genetic polymorphisms including the major histocompatibility complex (MHC) region. Since the early 1980s, familial occurrence of aPL with or without clinical manifestations of APS has been reported, and many researchers have investigated the immunogenetic predisposition to aPL or APS, including the role of HLA region which is involved in the control of immune recognition and the following response.

It is now widely recognized that the most common autoantigens for aPL are β_2-glycoprotein I (β_2-GPI) and prothrombin. In particular, the molecular structure and properties of β_2-GPI have been intensively studied. A number of polymorphisms of β_2-GPI gene have been described, and the biological significance and its relation to anti–β_2-GPI antibodies have been discussed.

Further, thrombotic genetic factors, as additional risks for the onset of thrombotic events, have been examined in patients with aPL.

In this chapter, we summarize family studies on APS and describe several disease-susceptible genetic factors that have been evaluated in patients with APS, including HLA haplotypes, β_2-GPI gene, and other genetic variants on disease development.

Family Studies

The first description regarding familial occurrence of aPL, reported by Exner et al [1], showed 2 pairs of siblings with lupus anticoagulant (LA). Subsequently, Matthey et al [2] described primary APS in 4 members of 1 family and Cevallos et al [3] reported the development of primary APS in 1 woman whose identical twin sister was an asymptomatic carrier of aPL.

The first degree relatives of patients with systemic lupus erythematosus (SLE) or primary APS had a higher incidence of anticardiolipin antibodies (aCL) [4, 5], suggesting that a genetic predisposition may influence the appearance of aPL. Evidence of familial form of APS could be obtained by the identification of several kindreds with an increased frequency of aPL and/or clinical manifestations of APS. In 1987, Mackie et al [6] reported 3 families having more than 1 member with LA and called familial lupus anticoagulants [6]. Later on, Ford et al reported a large kindred in which 9 out of 23 members of 4 generations (4 had neurologic symptoms and 5 asymptomatic) were positive for LA [7]. Primary APS, in the absence of SLE, was also reported to cluster in families and has been described as familial primary antiphospholipid antibody syndrome [8, 9]. Goel et al [10] studied clinical and laboratory abnormalities in 7 families with more than 1 affected members with segregation analysis. They proposed a set of criteria for a familial form of APS and suggested that a susceptibility gene is inherited in an autosomal dominant pattern.

Many family studies have explored familial aPL or APS with a documented HLA linkage [6, 11–17], suggesting that haplotypes containing either DR4, DR6, or DR7 related phenotype/genotype have some sort of link to aPL production. However, some affected family members were clinically and serologically normal despite of sharing the HLA haplotype with aPL positive siblings [13, 14], postulating that HLA contributions are not the only determinant of aPL production or development of APS.

HLA Haplotype and aPL

HLA class II (DP, DQ, and DR) loci is located on chromosome 6, being the main function of this locus to mediate specific T lymphocyte dependent immune responses. HLA associations with SLE and autoantibodies in SLE have been extensively studied in various ethnic groups.

The HLA associations with aPL are the center of interest due to the clinically relevant prothrombotic effects of these autoantibodies. Asherson et al [18] reported the increased frequency of DR4 in 13 patients with primary APS in a British population, data confirmed by Camps et al [19] in a population from the south of Spain and by Goldstein et al [20] in Canadian patients. HLA DR4 is typically in linkage disequilibrium with HLA-DQB1*0302 (DQ8) or DQB1*0301 (DQ7) [21]. Vargas-Alarcon et al [22] found that HLA DR5 was increased in 17 Mexican patients with primary APS. However, considering the antigen heterogeneity of aPL, specific autoantibody subgroup analysis needs to be done.

Studies of HLA alleles in patients with conventional aCL showed increased frequencies of HLA DR4 [23–25] or DR7 [19, 26] in SLE population. DR7 was also increased in Mexican patients with aCL [27]. After a specific β_2-GPI-based ELISA assay became available, positive correlations were found between anti–β_2-GPI antibodies and DQB1*0604/5-DRB1*1302 in African Americans, DR4-DQB1*0302 in white/Mexican Americans [28], and DRB1*0901 in Japanese [29]. Galeazzi et al [30] showed increased frequency of DRB1*0402/3 and DQB1*0302 in a large series of European lupus patients with anti–β_2-GPI antibodies. These studies were done in SLE or mixture population. In patients with primary APS, we [31] showed in a detailed haplotype analysis that HLA DQB1*0604/5/6/7/9-DQA1*0102-DRB1*1302