GENETIC RISK FACTORS ASSOCIATED WITH ANTIPHOSPHOLIPID SYNDROME

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ABSTRACT

Antiphospholipid syndrome (APS) is characterized by venous or arterial thromboses, fetal losses and thrombocytopenia, in the presence of antiphospholipid antibodies (aPL), namely lupus anticoagulant (LA), anticardiolipin antibodies (aCL) or antibodies directed to various proteins, mainly beta2-glycoprotein 1 (β2-GP1), or in the presence of all three. It is possible that some people with APS have a genetic predisposition for developing this syndrome. Genetic susceptibility related to aPL and APS has been extensively examined during recent years. It is becoming increasingly clear that interactions between more than one genetic abnormality or between a genetic factor and environment components determine whether and when an individual will suffer from venous thrombosis. Given the fact that APS is characterized mainly by the presence of thromboembolic events, it seems perfectly plausible that several genetic factors may also be involved in its pathophysiology. Despite the strong association between aPL and thrombosis, their pathogenic role in the development of thrombosis has not been fully elucidated. This review focuses on some of the genetic risk factors associated with APS.

Keywords: genetics, antiphospholipid antibody, antiphospholipid syndrome

There are two main classifications of antiphospholipid syndrome (APS): **primary,** if APS is not associated with other autoimmune disorder, such as systemic lupus erythematosus (SLE); **secondary,** if APS is associated with SLE or another autoimmune disorder. Antiphospholipid syndrome is diagnosed when arterial or venous thrombosis or recurrent miscarriages occur in a person in whom laboratory tests for antiphospholipid antibodies (APL) [anticardiolipin antibodies (aCL) and/or lupus anticoagulant (LA) and/or anti-b_2-glycoprotein 1 antibodies (anti-b_2-GP1] are positive. These antibodies must be present in the patient's blood at least two times in tests that are performed twelve weeks apart (1).

Antiphospholipid antibodies have been found in approximately 12% of elderly populations and in some 2% of younger populations. Some evidence favors natural autoantibodies perhaps having specific regulatory functions in the immune system. In accordance with these observations, it may be possible that autoantibodies are not pathological forms of immunity but, under aberrant vascular conditions such as oxidant stress, they lose their normal functions, leading to autoimmunity (2).

Genetic factors are hypothesised to play a role in the susceptibility to APS based on several family studies in patients with aPL and/or clinical manifestations of APS (3). Familial clustering of raised aPL antibody levels and HLA linkages indicate that the antibodies probably occur in genetically susceptible hosts in response to some antigenic challenge. No specific gene or inheritance pattern has been linked to the genetics of APS. However, it has been identified that this disorder has occurred in several members of the same family. Many people who have APS, however, do not have another autoimmune disorder, and their disease is referred to as primary APS. The possibility of a genetic predisposition to develop the APS and to produce aCL and LA has been addressed by family studies and by population studies. Various studies suggested a familial occurrence of aCL and LA, with or without clinical evidence of APS. This familial tendency could be genetically determined. Multiple human leukocyte antigen -DR or -DQ associations with

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aPL have been described. Genetic studies of beta$_2$-glycoprotein 1 (b_2-GP1) polymorphisms have been determined and Val/Leu polymorphism could be a genetic risk for having anti-b_2-GP1 and APS. Compared with polymorphism of b_2-GP1 as a genetic risk factor for APS, b_2-GP1 deficiency is not associated with thrombosis and patients with APS usually have normal or somewhat elevated levels of b_2-GP1. The V-encoding allele and the homozygous VV genotype at position 247 of the β_2-GP1 gene may play a role in the generation of anomalous β_2-GP1, with consequent auto-antibody production, and in phenotype expression of arterial and venous thrombosis in APS patients (4,5).

The physiological function of β_2GP1 has not been established; it has been suggested that the protein may play a scavenging role for exposed anionic phospholipid after apoptosis. Moreover, the presence of aPL is linked to genetic predisposition, which may be associated, at least in part, with genes of the major histocompatibility complex (HLA system) (6).

The genetics of b_2-GP1, one of the most representative target antigens of aPL, has been extensively studied. A genetic polymorphism of the β_2-GP1 is recognized by aPL and may even play a role in the development of APS. Regarding the genetics of β_2-GP1, there is evidence that the Val247 allele may be one of the genetic risk factors for development of APS – although the results are contradictory. The Val247 β_2-GP1 allele was associated with both a high frequency and stronger reactivity of anti-β_2-GP1 (7,8).

On the other there is no association between the Val/Leu247 polymorphism and the presence of anti-β_2-GP1 in a white population (9,10).

Exposure to one or more environmental agents, such as infections, in a genetically susceptible individual, through a molecular mimicry, can result in the production of pathogenic aPL that can induce thrombosis and pregnancy loss. Another study has reported a familial occurrence and apparent autosomal dominant inheritance with variable clinical expression in which familial aggregation of this disorder may be common and a genetic basis may be involved in its pathogenesis. Multiple HLA-DR or -DQ associations with aPL have been described, but are difficult to interpret because of small patient sample size and questions regarding appropriate ethnically-matched control populations. In a study of 13 patients with the primary form of APS, HLA-DR4 and DRw53 were more frequently found, but no correction was made for multiple comparisons. Subsequent studies from this group suggest that co-existence of C4 deficiency alleles with DQB1 alleles that contain the TRAELDT structural domain seems to be associated with aCL. As a result, polymorphisms on or near the phospholipid binding site or the antigenic site can affect autoantibody production (11,12).

In one study anti-b_2-GP1 and proteina S (PS) were correlated with each other and dual reactivity to b_2-GP1 and PS was associated only with an increased history of thrombotic events in APS (13).

A study hypothesized that anti-endothelial protein C receptor (EPCR) autoantibodies may be involved in clinical manifestations of APS and in fetal loss (14).

Results of early genetic studies have established that two types of genetic defects cause venous thrombosis: loss-of-function mutations (antithrombin [*SERPINC1*], PC [*PROC*] and PS [*PROS1*]) and gain-of-function mutations (Factor V Leiden [*F5*] G1691A and prothrombin [*F2*] G20210A) (15).

The prevalence of two prothrombotic genetic factors (*F5* G1691A and *F2* G20210A) was increased in patients with aPL with a history of venous/arterial thrombosis compared to patients with aPL without history of thrombosis (16).

The studies showed that the *F13A1* Leu34 allele had no protective effect in the development of thrombosis in patients with APS. On the contrary, found that this polymorphism was associated with a higher risk of thrombosis in patients with the presence of both aPL and high fibrinogen levels (17).

Another study on the *ANXA5* polymorphism (*ANXA5*-1C-T) and the presence of anti-annexin A5 antibodies in APS concluded that the detection of these antibodies does not seem relevant for estimating the risk for thrombosis or miscarriage in APS (18).

The gene encoding P-selectin glycoprotein ligand-1 (*SELPG*) and showed that a VNTR polymorphism on this gene is a significant determinant of thrombosis predisposition in patients with APS (19).

Genome-wide linkage analysis and larger cohort studies would lead to better understanding of the genes that might be involved in APS (3).

However, it has been difficult to determine genetic risk factors for aPL and APS because of the heterogeneity in the antigen specificity and the pathogenesis of clinical manifestations related to APS. Given the fact that APS is characterized mainly by the presence of thromboembolic events, it seems perfectly plausible that several genetic fac-

tors may also be involved in its pathophysiology. The knowledge of these new pathogenic approaches might identify novel therapeutic targets and therefore may improve the management of these patients.

CONCLUSION

Genetic factors are thought to play a role in the susceptibility to APS, and identifying the gene(s) that predisposes an individual to develop it could lead to a better understanding of the diseases, as well as improved therapies. However, the genes involved in APS have not been identified because antigen specificity of aPL, highly heterogeneous and multifactorial. APS is still seen as a rather obscure disease despite extensive research.

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