Ethnic and geographical variation in antiphospholipid (Hughes) syndrome

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Table 1 summarises the prevalence and isotype distribution of anticardiolipin antibodies (aCL) and lupus anticoagulant (LA) in different populations of patients with primary APS and patients with SLE, mainly providing a point prevalence of these antibodies in various populations. It is evident from this that these antibodies occur in all populations of patients with SLE and primary APS studied, but with highly variable point prevalence.

A relative paucity of IgG (2%) and IgM (2%) aCL in Afro-Caribbean patients with SLE was noted and warrants further study. SLE in African-Americans and Afro-Caribbean patients with SLE is characterised by a generally worse outcome and a higher prevalence of autoantibodies than in other ethnic or geographical groups, and it would be of interest to determine if aPL are an exception to this pattern in SLE. In a largely Afro-American obstetric prenatal clinic population, the prevalence of IgG aCL was 1.25% which approximates the frequency of IgG aCL found in other unselected prenatal clinic populations. In general, most studies from various countries report a mixture of aCL isotypes in individual patients, with IgG aCL being the commonest and most closely associated with thromboses and fetal losses.

"IgG aCL are the commonest isotypes in most patients with SLE"

IgA aCL are rarely present alone, except in Afro-Caribbean patients with SLE. In African-American patients with SLE, IgA aCL are also common, but often coexist with other isotypes. The value of IgA aCL and their relationship with thrombotic events is still controversial. Some experimental work suggests that IgA aCL are as prothrombotic as the IgG or IgM isotypes. Although some reports showed that testing for IgA aCL was of additional benefit in patients with APS, especially in certain ethnic groups, other authors could not support these data.

Gharavi et al were the first to determine the distribution of immunoglobulin isotypes and phospholipid specificities of aCL in 40 patients with one or more of the following "aPL-associated clinical complications"—namely, thrombosis, fetal loss, and thrombocytopenia. They found IgA aCL in 52% of their population.

**Antiphospholipid antibodies (aPL)**

Routine screening for aPL now occurs in systemic lupus erythematosus (SLE) clinics because of the strong experimental and clinical evidence of the procoagulant nature of aPL and the demonstrations that anticoagulation provides effective secondary prophylaxis of thrombosis or pregnancy loss in patients with aPL.

Antiphospholipid antibodies (aPL) are recognised as a group of antibodies whose specificity is directed not only towards phospholipids such as cardiolipin but also towards phospholipid binding proteins such as (β2-glycoprotein I (β2-GPI) and prothrombin (PT)) or the complexes of phospholipids and phospholipid binding proteins. The presence of aPL is associated with arterial/venous thrombosis, recurrent fetal loss, neurological disorders, pulmonary hypertension, and thrombocytopenia. The term "antiphospholipid syndrome" (APS) or "Hughes syndrome" was coined to link these clinical manifestations with the persistence of aPL, which are now recognised as one of the most common causes of acquired thrombophilia.

Investigation of the clinical epidemiology of APS is in its early stages. During the past 20 years, studies of aPL and APS have been made in many countries and ethno-geographical groups. aPL appear to occur in all populations studied, with some variations noted in their frequency and in the clinical complications. Environmental and genetic factors contribute to ethnic variation and susceptibility to APS and thus interethnic differences in disease patterns may be due to environmental or genetic factors, or both.
Only one patient had IgA aCL as the sole aPL; thus it was concluded that this test is useful to identify occasional patients with APS. Molina et al. studied 152 African-American, 136 Afro-Caribbean (Jamaican), and 163 Hispanic (Colombian) unselected patients with SLE. The major finding of their study was the higher prevalence of IgA aCL in the Afro-Caribbean population (21%), IgA aCL being the sole isotype, detected in 82% of these positive patients. This isotype was usually detected at low titres and did not seem to be associated with clinical features of APS. However, in 1999 Diri et al. reported eight African-American female patients with the APS, in whom IgA aCL were present in seven, co-occurring with IgG or IgM isotype in four of them.

In the same study they also found IgA anti-β2GPI in 4/8 patients, co-occurring with IgM isotype in three of them.

In a cross-sectional study to determine the prevalence of IgA aCL and anti-β2GPI and study their clinical significance in a cohort of 134 patients with SLE, we found a low prevalence (13%) of IgA aCL in patients with SLE. It is not clear whether the African origin or ancestry of these populations correlates with the autoantibody profile. It would seem likely that methodological, and possibly, environmental factors underlie the variations that occur in the aCL isotypes among these populations. Whether IgA aCL might contribute to a more comprehensive identification of APS in some SLE populations is still controversial.

### Table 1: Prevalence and isotype distribution of aCL and LA in different populations of patients with primary APS and SLE

<table>
<thead>
<tr>
<th>Reference</th>
<th>Ethnicity or country</th>
<th>Any aCL isotype</th>
<th>IgG aCL (%)</th>
<th>IgM aCL (%)</th>
<th>IgA aCL (%)</th>
<th>LA (%)</th>
<th>Correlation with thrombosis and/or fetal loss</th>
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<tr>
<td>European</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>Sturfelt et al. (1987)**</td>
<td>Sweden (59)</td>
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<td>No</td>
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<td>Stefani et al. (1991)**</td>
<td>Italy (64)</td>
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<td>44</td>
<td>9</td>
<td>NA</td>
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<td>Gourley et al. (1996)**</td>
<td>Ireland (95)</td>
<td>44</td>
<td>31</td>
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<td>Europe (1574)</td>
<td>NA</td>
<td>23</td>
<td>14</td>
<td>14</td>
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<td>Cervera et al. (2002)**</td>
<td>Europe (1000)</td>
<td>87.9</td>
<td>43.6</td>
<td>12.2</td>
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<td>53.6</td>
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<tr>
<td>American (North, South)</td>
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<td></td>
<td></td>
<td></td>
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<td>Wilson et al. (1988)**</td>
<td>Black American (44)</td>
<td>27</td>
<td>100</td>
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<td>Alarcón-Segovia et al. (1990)**</td>
<td>Mexico (500)</td>
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<td>39</td>
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<td>Cervera et al. (1999)**</td>
<td>Brazil (147)</td>
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<td>20</td>
<td>5.5</td>
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<td>NA</td>
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<td>Molina et al. (1999)**</td>
<td>Afro-Caribbean (136)</td>
<td>21</td>
<td>2</td>
<td>2</td>
<td>2</td>
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<tr>
<td>Alarcón et al. (1999)**</td>
<td>Hispanic (70)</td>
<td>7</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>Alarcón et al. (1999)**</td>
<td>African-American (88)</td>
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<td>NA</td>
<td>NA</td>
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<td>Alarcón et al. (1999)**</td>
<td>Caucasian (71)</td>
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<td>Diri et al. (1999)**</td>
<td>African American (8)</td>
<td>100</td>
<td>75</td>
<td>87.5</td>
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<td>Cucurull et al. (1999)**</td>
<td>African American (100)</td>
<td>33</td>
<td>18</td>
<td>7</td>
<td>24</td>
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<td>Cucurull et al. (1999)**</td>
<td>Colombian (140)</td>
<td>25</td>
<td>18</td>
<td>13</td>
<td>15</td>
<td>NA</td>
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<td>Cucurull et al. (1999)**</td>
<td>Spanish (160)</td>
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<td>15</td>
<td>16</td>
<td>NA</td>
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<td>Aguirre et al. (2001)**</td>
<td>Chilean (129)</td>
<td>30</td>
<td>16</td>
<td>14</td>
<td>8</td>
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<tr>
<td>Asian</td>
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<td>Saluja et al. (1999)**</td>
<td>Indian (76)</td>
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<td>NA</td>
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<td>Jones et al. (1991)**</td>
<td>Malaysia (200)</td>
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<td>Wong et al. (1991)**</td>
<td>China (91)</td>
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<td>44</td>
<td>1</td>
<td>4</td>
<td>11</td>
<td>No</td>
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<tr>
<td>Wong et al. (1991)**</td>
<td>China (91)</td>
<td>46</td>
<td>44</td>
<td>1</td>
<td>4</td>
<td>11</td>
<td>No</td>
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<tr>
<td>Ninomiya et al. (1992)**</td>
<td>Japan (349)</td>
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<td>Saxena et al. (1994)**</td>
<td>Indian (70)</td>
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<td>Tsutsumi et al. (1996)**</td>
<td>Japan (308)</td>
<td>NA</td>
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<td>Shrivastava et al. (2001)**</td>
<td>India (76)</td>
<td>51</td>
<td>51</td>
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<td>5</td>
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<td>No</td>
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<td>Malaviya et al. (1996)**</td>
<td>Kuwait, Middle-Eastern and North African Arabs (29)</td>
<td>75</td>
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<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Yes</td>
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<td>Al Maini et al. (2002)**</td>
<td>Gulf Arabs and Arabs of Persian descent (83)</td>
<td>NA</td>
<td>17.3</td>
<td>14.2</td>
<td>NA</td>
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<td>Houman et al. (2004)**</td>
<td>Tunisan (North Africans) (100)</td>
<td>66</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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* IgG and IgM aCL or LA, or both; † patients from seven European countries: 97.7% white, 2.3% other races; ‡ in-house ELISA test done at Louisiana State University Health Sciences Center in New Orleans; § Lupus in Africa Study Group: Lupus in African populations: Nature nurture. From University of Alabama at Birmingham, University of Texas-Houston Health Science Center, and University of Texas Medical Branch at Galveston; *both studies from All India Institute of Medical Sciences, New Delhi; †† population comprised 164 Chinese, 26 Malay, and 10 Indian. No differences were found in the prevalence of raised aCL between the three ethnic groups. NA, data not available.
group; its frequency was increased more in primary APS than in secondary APS, the association being even stronger in anti-β2GPI positive primary APS. Accordingly, it is suggested that this (DQB1*0604/5/6/7/9-DQA1*0102-DRB1*1302) haplotype predisposes to anti-β2GPI, which is one of the most specific markers of APS. HLA-DR and DQ molecules function by binding specific peptides with subsequent presentation by antigen presenting cells to regulatory or effector T cells. Our data may be viewed in this context and suggest that a molecule encoded by the DQB1*0604/5/6/7/9-DQA1*0102-DRB1*1302 haplotype may preferentially present peptides derived from β2GPI or associated molecules. Consequently, people bearing this haplotype may be prone to generate anti-β2GPI after taking other genetic and environmental variables into account.

In addition to these classic class II molecules, it has recently been shown that HLA-DM molecules have crucial roles in HLA class II restricted antigen presentation, by studies of cell lines lacking HLA-DM, which are defective in class II restricted antigen processing. The presence of polymorphisms in DM genes raised the possibility of their involvement in the development of HLA class II associated diseases, although the relation between these polymorphisms and the function of DM molecules has not yet been clarified.

A study of SLE in a Japanese population did not find any significant association between the HLA-DM polymorphisms and the development of SLE and specific manifestations, but the existence of aPL was not considered. We have recently examined the susceptibility of these polymorphisms to aPL production in a white British population, and observed the skewed distribution of DMA alleles including an increase of DMA*0102 in patients with aPL, which is the first report on HLA-DM and aPL/APS. The minor effect of the DMA polymorphisms on the presence of antiprothrombin antibodies (aPT), especially of IgG class, suggested the importance of another genetic predisposition to aPT production. More than half of aPL positive patients did not have DMA*0102, indicating the involvement of other genetic risk factors for aPL production separate from the DMA*0102 or DMA*0102 containing haplotype. Furthermore, the presence of a considerable number of patients with DMA*0102 but without aPL suggests the requirement of a coexistence of other genetic or environmental (for example, infections) factors for aPL production.
"Different HLA polymorphisms associated with APS may lead to development of different aspects of the disease."

We conclude that several HLA class II gene polymorphisms are associated with APS, probably along with other genetic factors, and may determine the development of different aspects of the disease. These polymorphisms may be correlated with the immune response against thrombosis related autoantigens, such as phospholipid binding proteins and phospholipids. It is also possible that some undefined polymorphisms in linkage disequilibrium with the HLA region are responsible for the induction of anti-β2GPI antibodies.

**POLYMORPHISMS OF TARGET ANTIGENS AND COAGULATION FACTORS**

Polymorphisms of target antigens and coagulation factors are reported (table 3) to be associated with aPL induction and the development of thrombosis.

The human β2GPI gene is located on chromosome 17 and so far four common single nucleotide polymorphisms in protein coding region have been identified. The polymorphisms Ser/Asn 88, Val/Leu 247, Cys/Gly306, and Trp/Ser 316 are located in exons 3, 7, 7, and 8 of the β2GPI gene, respectively. The Val/Leu polymorphism at codon 247 has been extensively studied among these polymorphisms. Hirose et al reported that Val 247 alleles were found more frequently in Asian patients with APS than among controls, although Val 247 alleles were more common in the white or the black patients with APS with appropriate clinical heterogeneity. Camilleri et al found no association Val/Leu 247 polymorphism and the presence of anti-β2GPI in a white population.

**LIMITATIONS OF GENETIC STUDIES IN APS**

Interpretation of epidemiological studies in various ethnic groups is quite difficult for the following reasons:

- Although the enzyme linked immunosorbent assay (ELISA) for aCL antibodies and LA testing has been extensively standardised, significant variation between laboratories in the results of testing still remains. The precise cut off points for positive/negative results vary among laboratories.
- Clinical heterogeneity: the clinical definition of APS has varied among studies. Some patients with APS also manifest SLE, and constitute a heterogeneous population, making it difficult to analyse the role of a single factor. With the publication of the Sapporo criteria for the preliminary classification criteria for definite APS this problem will be solved with studies done on more uniform patient groups.
- Interethnic variation in the associations of aPL with thrombosis or pregnancy loss must also take into account the multiple risk factors that exist in most populations for these complications. Possibly, variation in such collateral risk factors—for example, drug use or genetic risk factors for thrombosis, may influence complication rates associated with aPL in various populations. For instance, in Lebanon, a high prevalence of prothrombin G20210A and factor V Leiden mutations exists. These factors will increase the thrombotic risk, especially in patients with aPL.
- Disease activity: The level of disease activity is an important factor to control for in future studies. In early studies in the African-American clinic population in New York, a high prevalence of aPL was associated with a high level of disease activity.
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Orleans it was found that IgG aCL were present in 27% of patients with SLE during periods of disease activity, compared with only 5% of patients with SLE during periods of less active SLE.

- Geographical migration: with the current increasing geographical migration and intermingling across geographical and ethnic groups, it is important to consider these variables in the interpretation of future studies.

CONCLUSIONS

Genetic susceptibility related to aPL and APS has been extensively examined in past years. However, it has been difficult to determine genetic risk factors for aPL and APS because of the heterogeneity in the antigen specificity, and pathogenesis of the clinical manifestations of APS. It is clear from the above that the study of the clinical epidemiology of APS in different ethnic and geographical groups is of particular relevance.

The publication in 1999 of international consensus criteria for APS should facilitate comparisons or patient selection. The publication in 1999 of international consensus criteria for APS should facilitate comparisons or patient selection. The publication in 1999 of international consensus criteria for APS should facilitate comparisons or patient selection. The publication in 1999 of international consensus criteria for APS should facilitate comparisons or patient selection. The publication in 1999 of international consensus criteria for APS should facilitate comparisons or patient selection.

**REFERENCES**


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