17 ISCHEMIC VASCULAR DISEASE AND ANTIPHOSPHOLIPID ANTIBODIES ARE ASSOCIATED WITH HLA-DRB1 *04/*13 ALLELES IN SYSTEMIC LUPUS ERYTHEMATOSUS

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Background Cardiovascular disease (CVD) is common in systemic lupus erythematosus (SLE) and SLE patients with antiphospholipid antibodies (anti-PL) are at particularly high risk. HLA-DRB1 genotypes are associated with SLE per se and have also been linked to pro-thrombotic anti-PL. The authors investigated a possible relationship between HLA-DRB1 genes, anti-PL and CVD in patients with SLE.

Methods A total of 665 unrelated SLE patients of Caucasian origin from three clinics and 1403 controls were included. Previous manifestations of objectively verified ischemic heart disease (IHD, angina and/or myocardial infarction), ischemic cerebrovascular disease (ICVD, stroke and/or transitory ischemic attacks) and any arterial event (IHD and/or ICVD and/or ischemic peripheral arterial disease) were retrieved through patient interviews and medical records. Anti-PL in sera of patients were measured with ELISA. Two-digit HLA-DRB1 typing was performed in patient and control individuals by sequence-specific primer-PCR. Meta-analyses, presented below, of the combined results were calculated with RevMan 5.

Results The authors identified 67 patients with IHD, 78 with ICVD and 139 with any previous arterial event**.** HLA-DRB1*04

was not enriched in SLE per se, but was more frequent among SLE patients with ICVD (OR:1.88, 95% CI:1.16 to 3.05). HLA-DRB1*04 was furthermore associated with all measured specificities of anti-PL: anticardiolipin(CL) IgG (OR: 1.99, 95% CI:1.35 to 2.93), and IgM (OR: 1.76, 95% CI:1.20 to 2.58), anti-$\beta_2$glycoprotein-1(β_2GP-1) IgG (OR: 2.66, 95% CI:1.81 to 3.91), antiprothrombin IgG (OR: 1.69, 95% CI:1.04 to 2.76) and with a positive lupus anticoagulant test (OR:2.57, 95% CI:1.53 to 4.32). Additionally HLA-DRB1*13 was associated with anti-β_2GP-1 IgG (OR: 1.69, 95%CI:1.13 to 2.52) and antiprothrombin IgG (OR: 1.66, 95% CI:1.01 to 2.75) antibodies. Carriers of the combined genotype HLA-DRB1*04/*13 were at especially high risk for any arterial event (OR: 4.02, 95% CI1.74 to 9.30) and were frequently diagnosed with positive tests for anti-CL IgG (OR: 3.52, 95% CI 1.68 to 8.71) as well as for anti-β_2GP-1 IgG (OR: 3.18, 95% CI1.36 to 7.42). The previously reported associations between SLE and HLA-DRB1*03 and HLA-DRB1*15 were confirmed (OR>2), but neither of these HLA-alleles were associated with CVD in our study.

Conclusion Our results demonstrate that a subgroup of SLE patients, carriers of HLA-DRB1*04, have enhanced risk of ICVD. Prothrombotic anti-PL, associated with HLA-DRB1*04 and to a less extent with HLA-DRB1*13, possibly constitute an underlying mechanism. A potential interaction between DRB1*04 and DRB1*13 is suggested by the fact that the combined genotype (*04/*13) conferred a high risk of several anti-PL and of any arterial event. This study illustrates the importance to investigate subgroups of clinically well-defined patients when evaluating genetic contributions to autoimmune diseases.