Conclusion Our study confirmed association of DRB1*04 alleles not only with susceptibility to RA but with clinical features of the disease as well.

THU0005 INCREASED FREQUENCY OF HLA DR 11 AND DECREASED FREQUENCY OF HLA DR 1 IN CAUCASIAN EUROPEANS WITH ABDOMINAL AORTIC ANEURYSMS

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10.1136/annrheumdis-2001.108

Background A genetic predisposition has been reported to play a key role in the pathogenesis of abdominal aortic aneurysms (AAA) in Japanese and a subgroup of North American patients with inflammatory AAA.

Objectives The aim of this study was to evaluate a possible association of HLA DR phenotypes with AAA in a European population sample.

Methods Consecutive patients with AAA larger than 3 cm presenting at our outpatient clinic were analysed for HLA class II genotypes using the PCR-SSP technique at low resolution level. DR phenotypes were deduced from these results. Patients with any history of an autoimmune disease were excluded from the study. The frequencies of HLA DR phenotypes were compared to those of a cohort of consecutive and ethnically matched organ donors using the appropriate statistical methods. Classification trees have been applied to increase the predictive value and to consider more than one variable.

Results HLA DR genotyping was performed in 54 European AAA patients (44 males) and 296 controls (203 males). At the HLA DRB1* locus, 19/54 AAA patients (35,2%) and 63/296 controls (21,3%) were found to be 1*11 positive ($p = 0,035$; OR = 2,01, 95% c.i.: 1,08–3,75). Subanalysis of male patients revealed 17/44 (38,6%) AAA patients and 39/203 (19,2%) in controls to be 1*11 positive ($p = 0,009$; OR = 2,65, 95% c.i.: 1,31–5,33). Regarding HLA DRB1*01, 4/54 AAA patients (7,4%) and 64/296 controls (21,6%) turned out to be 1*01 carrier ($p = 0,014$; OR = 0,29, 95% c.i.: 0,10–0,83). Subanalysis of male patients revealed 2/44 (4,5%) and 48/203 (23,6%) DRB1*01 carrier in AAA patients and controls, respectively ($p = 0,003$; OR = 0,15, 95% c.i.: 0,04–0,66). No associations for DRB1*11 and 1*01 were observed in female patients.

Conclusion These data suggest a positive association between AAA and DR 11 and a possible protective effect of DR 1 in male Caucasian Europeans suffering from AAA. This finding supports the hypothesis that MHC class II genes play a role in the pathogenesis of AAA.

THU0006 DQB1 POLYMORPHISM IN RHEUMATOID ARTHRITIS PATIENTS WITH SHARED EPITOPE-NEGATIVE DRB1 ALLELES

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10.1136/annrheumdis-2001.109

Background The association of rheumatoid arthritis (RA) with HLA-DRB1 alleles sharing sequences in the third hypervariable region has been reported in several investigations, but genetic

analyses suggest the possible involvement of other HLA class II genes in conferring susceptibility.

Objectives We have investigated the distribution of HLA-DQB1-DRB1 polymorphism in 87 RA patients from southern Croatia and 141 healthy controls. RA patients were predominantly females (83 females vs 5 males).

Methods All patients and controls were tested for HLA class II alleles (DRB1, DQA1, and DQB1) by PCR-SSP method.

Results Distribution of predisposing DRB1 alleles according to the shared epitope (SE) model showed that 11 patients were homozygous for the predisposing alleles. Additional 48 patients carried one of the SE predisposing alleles (*0101, *1001, *0401, *0404, *0405, *0408). Distribution of DQB1 alleles among patients with SE-positive DRB1 alleles revealed that all DRB1*0101 and *1001 patients were DQB1*0501 positive. Among twenty patients with SE-positive DRB1*04 alleles, three different DQB1 alleles were observed (DQB1*0301, *0302 and *0201). Remaining 26 patients with SE-negative DRB1 alleles were additionally analysed for the presence of DQB1*0301, *0302 and *0201 alleles. All eight patients with SE negative DRB1*04 alleles (DRB1*0402, *0403, *0407) were DQB1*0302 positive. Among the remaining non DRB1*04 patients, 16 were either DQB1*0301 or *0201 and only two patients did not carry neither DQB1*0301 nor *0201.

Conclusion These data suggest that in patients with SE negative DRB1 alleles, DQB1*0301, *0302 and *0201 alleles should be considered as a genes contributing to the RA predisposition. DQB1*0301, *0302 and *0201 alleles should be considered as a genes contributing to the RA predisposition.

THU0007 ASSOCIATION OF HUMAN MHC CLASS I AND CLASS II GENES WITH SUSCEPTIBILITY TO SYSTEMIC LUPUS ERYTHEMATOSUS IN MALAYS AND CHINESE

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10.1136/annrheumdis-2001.110

Background Systemic lupus erythematosus (SLE) is a chronic autoimmune disorder. Its prevalence is higher in Chinese and Black populations compared to Caucasians. The prevalence of SLE in Malaysia is estimated to be 43/100,000 population.¹

Objectives The objective of this study was to investigate the association between SLE with the human MHC Class I and Class II genes.

Methods A modified PCR-SSP Methodology, known as Phototyping^{2,3} was carried out to determine the HLA-A, -B, -DR and -DQ genes of the subjects. 50 Malays and 50 Chinese patients with SLE fulfilling the ACR criteria were recruited along with 50 Malays and Chinese age- and race-matched controls.

Results Statistical analysis showed that both the Malay and Chinese have similar results despite minor differences. HLA-A11 is associated with SLE in both races, whereas HLA-DR12 has been found to be statistically significant as protective antigen specificity. Compared to Malays, Chinese SLE patients have a higher frequency of DR2 compared to the controls. DRB1 was only seen in Malay SLE patients (OR 8.69 compared to controls). DRB1*02 and DQB1*05 was only seen in Chinese SLE patients (OR 2.41 compared to controls). Alleles negatively associated with SLE, possibly conferring a protective effect are as follows: In both Malay and Chinese SLE patients, DRB1*12,

DQB1*0301/4, in Malay SLE patients, DRB1*13, DRB3*0301, in Chinese SLE patients, DRB3*0201.

Conclusion These results differ from those obtained in other ethnic groups, i.e. suggesting a different disease pathogenesis.

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THU0008 TNF- α GENE POLYMORPHISM IN SEVERE AND MILD RHEUMATOID ARTHRITIS

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10.1136/annrheumdis-2001.111

Background TNF- α is thought to be the key driving cytokine in Rheumatoid Arthritis (RA) and recently became a therapeutic target for treatment of patients particularly resistant to conventional therapy. In our study we looked for a genetic background that should indicate some criteria to address RA patients towards more aggressive treatments with anti-TNF- α agents.

Objectives We assessed the role of the -238 and +489 TNF- α gene polymorphisms in a series of patients with severe aggressive disease who were treated with anti-TNF- α therapy because of their poor response to a DMARDs combination strategy. The phenotypes of these patients were compared to those of a cohort of patients who had a good response to Methotrexate (MTX), thus revealing a mild/moderate disease.

Methods One hundred and thirty-eight (138) RA patients and sixty-four (64) controls (Healthy Blood Donors, HBD) entered the study. RA patients were divided into 2 subgroups. Group A: 72 rheumatoids, called MTX-responders (MTX-R), who were in stable partial remission since at least six months after MTX treatment (15 mg/w weekly, range 10–25 mg/w). Stable partial remission was defined when patients had less than 3 swollen joints and a morning stiffness of less than 20'. Group B: 68 rheumatoids with still active disease (more than 6 swollen joints and a morning stiffness of at least 60') despite 6 months of combination therapy (MTX + Sulphasalazine + Hydroxychloroquine or MTX + Cyclosporine, including low doses of prednisone, 5 mg/day). This group subsequently received anti-TNF- α therapy and was labelled as anti-TNF-treated, (TNF-T). Genotyping for -238 and +489 TNF- α polymorphisms was made according to Weiss *et al.*¹ Statistical analyses (Odds Ratio, 95% Confidence Interval) were performed using Prism Software (Graph-Pad, S. Diego, CA 92121-USA).

Results MTX-R had an overall frequency of GG homozygosity for the -238 polymorphism of 91.6% vs 92.2% in HBD, while in TNF-T subgroup the GG genotype had a frequency of 100% (OR = 13, CI = 0.7–240, p = 0.008 vs MTX-R). The comparison between TNF-T and HBD is similarly striking (POR = 12, CI = 0.7–230, p = 0.01). The major finding concerning the +489 polymorphism is the lower frequency of the AA genotype in RA in general (OR = 4.2, CI = 1–18, p = 0.01) and in TNF-T in particular.

Conclusion The GG genotype for the -238 TNF- α polymorphism marks all patients who received anti-TNF- α therapy. This group of patients also showed a significant reduction of the AA genotype of the +489 polymorphism. This latter finding supports the hypothesis that the A allele of the +489 TNF- α

intronic polymorphism is linked to a genetic setting that offers a less aggressive phenotype in RA.

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THU0009 FIBRONECTIN GENE POLYMORPHISM IN SEVERE AND MILD RHEUMATOID ARTHRITIS

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10.1136/annrheumdis-2001.112

Background The importance of Fibronectin (Fn) in RA chronic synovial inflammation is increasing. There are at least 6 restriction fragment length polymorphisms (RFLPs) described so far in the Fn gene, but very few is known about their possible functional relevance.

Objectives In this study we assessed the role of the Msp-I Fn gene polymorphism in a series of patients with severe aggressive disease who were treated with anti-TNF- α therapy because of their poor response to a DMARDs combination strategy. The phenotype of these patients were compared to those of a cohort of patients who had a good response to Methotrexate (MTX), thus revealing a mild/moderate disease.

Methods Seventy-nine (79) RA patients and sixty-one (61) controls (Healthy Blood Donors, HBD) entered the study. RA patients were split into 2 subgroups: 57 rheumatoids in stable partial remission (less than 3 swollen joints and a morning stiffness of less than 20') since at least six months after MTX treatment (15 mg/w weekly, range 10–25 mg/w), thus called MTX-responders (MTX-R) and 22 rheumatoids with still active disease (more than 6 swollen joints and a morning stiffness of at least 60') despite 6 months of combination therapy (MTX + Sulphasalazine + Hydroxychloroquine or MTX + Cyclosporine, including low doses of prednisone, 5 mg/day). This latter group received anti-TNF- α therapy and was then labelled anti-TNF-treated (TNF-T). Genotyping for the Msp-I Fn gene polymorphism was made according to Avila *et al.*,¹ who named C the allele resistant to enzyme's digestion and D the variant susceptible. Statistical analyses (Odds Ratio, 95% Confidence Interval) were performed using Prism software (Graph-Pad, S. Diego, CA 92121-USA).

Results MTX-R had an overall frequency of DD homozygosity of 56.1% vs 52.5% in HBD, while in TNF-T subgroup the DD genotype had a frequency of 81.8% (OR = 4.1, CI = 1.2–13, p = 0.008 vs HBD). The comparison between TNF-T and MTX-R is similarly striking (OR = 3.5, CI = 1.1–12, p = 0.01).

Conclusion The DD genotype for Msp-I Fn gene polymorphism marks the patients who received anti-TNF- α therapy and may lead to a more aggressive phenotype in RA.

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THU0010 VITAMIN D AND OESTROGEN RECEPTOR POLYMORPHISM IN RHEUMATOID ARTHRITIS

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10.1136/annrheumdis-2001.113