reaction-single strand conformation polymorphism (PCR-SSCP) coupled with sequencing analysis was used as the screening method for TAGAP variants.

Results Statistical significant difference was observed in Rs212389 alleles' distribution between RA patients and controls (p = 0.018, OR = 0.646, 95%CI: 0.449–0.930). No statistical significant difference was revealed in distribution of variants Rs394581 and Rs182429 between the studied groups.

Conclusions Our results confirm that the polymorphism Rs212389 confers the risk to RA liability in Europeans. However, more studies in larger groups of patients and controls and of multiple origins are needed as to confirm and increase the power of the suggested association.

A7.20 RESPONSE TO INFLIXIMAB THERAPY CAN BE PREDICTED USING DISTINCT, NON-OVERLAPPING GENE PANELS OF PERIPHERAL BLOOD GENE EXPRESSION IN RHEUMATOID ARTHRITIS AND CROHN'S DISEASE

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Background Biological therapies targeting tumour necrosis factor α (TNF-α) have been widely used to treat chronic inflammatory disorders including rheumatoid arthritis (RA) and Crohn's disease (CD). As these treatment modalities are rather expensive, there is a need for biomarkers that may predict therapeutic responses. As RA and CD have similar pathogenic background, one may expect to detect overlapping gene panels in predicting the response to the same therapy by the same approach. There have been very few studies using simultaneous pharmacogenomic approach in two diseases.

Methods In this study, we performed peripheral blood global gene expression profiling followed by Canonical Variates Analysis (CVA) in CD and RA to identify gene sets that can differentiate responders from non-responders for infliximab therapy; and validated the results in an independent cohort by RT-QPCR.

Results In CD, global gene expression analysis of samples obtained at baseline resulted in a list of 48 probe sets differentiating responders from non-responders. Comparing baseline and week 2 samples resulted in a list of five genes including AQP9, IGKC, MGAM, MMP8 and TNFAIP6 that exert expression changes upon treatment. Similarly, in RA, analysis of baseline samples resulted in a list of 30 probe sets that differentiated responders from non-responders. Expression of 3 genes; AQP9, IGJ and TNFAIP6 showed significant difference between baseline and week 2 samples. Results were validated by RT-QPCR on independent patient cohorts in both diseases. CVA analysis yielded to 15 and 12 genes in RA and CD, respectively, showing the best discriminatory power between responders and non-responders in both diseases, however there was no overlap between these two gene lists.

Conclusions We provided two pieces of proof of concept evidence showing that 1) peripheral blood gene expression profiles are suitable for determining gene panels with the highest discriminatory power in order to differentiate responders and non-responders in a patient cohort in CD and RA; and 2) distinct, non-overlapping gene panels are required for the prediction of the responder status in CD and RA despite the fact that these conditions have similar pathogenic background. Application of such gene panels could solve unmet needs in the clinical settings by determining specific responses to expensive biological therapies.

A7.21 SUPPRESSION OF HDAC5 EXPRESSION BY INFLAMMATORY CYTOKINES IS REQUIRED TO PROMOTE CXCL CHEMOKINE PRODUCTION IN RA FLS

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Background and Objectives Histone deacetylases (HDACs) are important regulators of gene expression and protein function in the immune system. HDAC inhibitors (HDACi) display anti-inflammatory properties in animal and in vitro models of rheumatoid arthritis (RA), as well as initial safety and efficacy in the treatment of systemic onset juvenile idiopathic arthritis. However, as most of the currently available HDACi display little selectivity or specificity for class I (HDAC 1–3, 8) and class II (HDAC 4–6, 9, 10) HDACs, the role of specific HDACs in RA is unclear. Here we examined the relationship between HDACs and inflammation in RA synovial tissue and fibroblast-like synoviocytes (FLS).

Materials and Methods RNA was isolated from arthroscopic synovial biopsies from 19 RA patients. MMP-1, TNFα, IL-6, and HDAC 1–10 expression was measured by quantitative PCR (qPCR). RA FLS were stimulated with IL-1β, TNFα and LP, S and HDAC expression was measured by qPCR RA FLS were transduced with adenovirus encoding control GFP or GFP-HDAC5 or transfected with control siRNA or siRNA targeting HDAC5. Effects of HDAC5 modulation on RA FLS gene expression were analysed by custom qPCR array.

Results Positive correlations were observed between RA synovial tissue expression of TNFα and HDAC1 (R = 0.651, P = 0.003) HDAC2 (R = 0.523, P = 0.022) and HDAC3 (R = 0.570, P = 0.011) and between MMP-1 and HDAC1 (R = 0.501, P = 0.029) and HDAC2 (R = 0.512, P = 0.025). A significant negative correlation was observed between synovial tissue expression of IL-6 and HDAC5 (R = –0.477, P = 0.039) and between clinical parameters of disease activity and HDAC5 (CRP: R = –0.664, P = 0.007; ESR: R = –0.556, P = 0.013: DAS28: R = –0.567, P = 0.011). HDAC5 mRNA expression was significantly and selectively reduced after RA FLS stimulation with TNFα and IL-1β, but not LPS. Of 84 genes regulated in RA FLS by IL-1β or TNFα, mRNA expression of CXCL9, CXCL10, and CXCL11 was selectively upregulated following silencing of HDAC5 expression. Conversely, mRNA expression of these chemokines was suppressed by overexpression of HDAC5 in RA FLS.

Conclusions RA synovial expression of HDAC 1 and 2, but not class II HDACs, positively correlates with local inflammatory mediators, while HDAC5 expression negatively correlates with IL-6 mRNA expression and with disease activity. HDAC5 mRNA is decreased after inflammatory stimulation, and silencing of HDAC5 leads to an increase of CXCL chemokine expression in RA. FLS, an effect reversed by HDAC5 overexpression. Our results suggest a protective role for HDAC5 in RA, and that HDACi which fail to target HDAC5 may be more promising for therapeutic applications.

A7.22 THE ETS1 TRANSCRIPTION FACTOR MAY PREDISPOSE TO RHEUMATOID ARTHRITIS SUSCEPTIBILITY

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Background and Objectives ETS1 is the founder member of ETS transcription factors' family which control the transcription of various immune related genes. The aim of this study was to identify if polymorphism ETS1 Rs11221332, described in Caucasian subjects, plays any role in rheumatoid arthritis (RA) susceptibility.
Materials and Methods We genotyped this polymorphism in 136 unrelated patients with RA and 147 healthy individuals with no history of autoimmune diseases. Genotyping was performed with polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) assay and the data were analysed by the SPSS statistical software.
Results Statistical significant difference was observed in the distribution of Rs11221332 genotypes between RA patients and controls ($p = 0.041$). Comparing Rs11221332 alleles' distribution between the studied groups the difference was higher [$p = 0.039$, (OR = 1.504, CI:1.036–2.183)].
Conclusions The present study revealed, for first time, the positive association of a polymorphism in the sequence of ETS1 transcription factor with RA susceptibility. Further studies in other ethnic group of patients are needed to confirm the results of the present genetic association study related to ETS1, a widely used transcription factor in the regulation of various genes' expression.

A7.23 THE HLA LOCUS CONTAINS NOVEL FOETAL SUSCEPTIBILITY ALLELES FOR CONGENITAL HEART BLOCK WITH SIGNIFICANT PATERNAL INFLUENCE

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Objective To identify foetal susceptibility genes in Ro/SSA autoantibody-mediated congenital heart block on chromosome six.
Methods Single nucleotide polymorphism (SNP) genotyping of individuals included in the Swedish Congenital Heart Block (CHB) study population was performed. Low resolution HLA-A, -Cw and -DRB1 allele typing was carried out in 86 families of the study population comprising 339 individuals (86 Ro/SSA autoantibody positive mothers, 71 fathers, 87 CHB index cases and 95 unaffected siblings).
Results A case-control comparison between index cases and population-based out of study controls (n = 1710) revealed an association of CHB with fifteen SNPs in the 6p21.3 MHC locus at a chromosome-wide significance of $p < 2.59 \times 10^{-6}$ (OR 2.21–3.12). In a family-based analysis between SNP markers as well as distinct MHC class I and II alleles with CHB we observed associations to HLA-DRB1*04 and HLA-Cw*05 variants that were significantly more often transmitted to affected individuals ($p < 0.03$ and $p < 0.05$, respectively), and HLA-DRB1*13 and HLA-Cw*06 variants which were significantly less often transmitted to affected children ($p < 0.05$ and $p < 0.04$). We further observed a significant association of increased paternal, but not maternal, HLA-DRB1*04 transmissions to the affected offspring ($p < 0.02$).
Conclusions Our study identifies HLA-DRB1*04 and HLA-Cw*05 as novel foetal HLA-allele variants that confer susceptibility to develop CHB in response to exposure to Ro/SSA autoantibodies, while DRB1*13 and Cw*06 emerged as protective alleles. For the first time, we also demonstrate paternal contribution to foetal susceptibility to CHB.

A7.24 THE PENTANUCLEOTIDE INSERTION IN HSPA1B GENE IS ASSOCIATED WITH IDIOPATHIC INFLAMMATORY MYOPATHY

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Background and Objectives The HSPA1B gene is one of the three HSP70 genes located within the Major Histocompatibility Complex (MHC) on chromosome 6p21. The HSP70 molecules in their intracellular form have antiapoptotic function and are responsible for stabilisation of protein structure; in their extracellular form, they act as mediators of immune response. The extracellular HSPs are part of the innate and adaptive immune response and are involved in the process of antigen presentation. The aim of our study was to find out if an association between polymorphisms of MHC located HSP70 genes and subgroups of idiopathic inflammatory myopathy exists.
Materials and Methods We have analysed 177 patients suffering from idiopathic inflammatory myopathy (82 patients with dermatomyositis – DM, 71 patients with polymyositis – PM, 22 patients with cancer associated myositis, 2 patients with inclusion body myositis) and 59 healthy controls. In total, six genetic polymorphisms located within the three HSP70 genes were analysed by direct genomic DNA sequencing. The statistical analysis was done using Fisher's exact test with calculated $p < 0.05$ considered as statistically significant.
Results and Conclusions The frequency of the "INS" allele of the pentanucleotide insertion polymorphism in HSPA1B (Rs9281590) was increased in patients suffering from myositis (43.79%) in comparison with controls (32.20%; $p < 0.05$). The Odds Ratio calculated for this polymorphism was 1.64 (CI95% 1.056; 2.545). Its increased frequency was predominantly found in DM patients ($p < 0.05$); the allele distribution in PM patients did not significantly differ from controls. Presence of INS allele was strongly related to the well described HLA associated risk, the HLA-DRB1*03 allele ($p < 0.001$), found mostly in PM patients. INS allele is independent on other myositis associated HLA allele, HLA-DRB1*16, found increased in the population of our DM patients. Other polymorphisms analysed in this study did not show any relation to the myositis. Our findings support the hypothesis, that DM and PM have partially different genetic background.
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A7.25 GENE-GENE INTERACTIONS IN INTERFERON PATHWAY GENE POLYMORPHISMS IN EUROPEAN AND AMERICAN SCLERODERMA COHORTS

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Background/Purpose Type-I interferon (IFN), a central mediator of innate immunity, has been shown to be the hallmark peripheral blood gene expression pattern in lupus (SLE) and a similar type-I IFN signature has been noted in systemic sclerosis (SSc). Interferon regulatory factor 5 and 7(*IRF5/IRF7*) and tyrosine kinase 2(*TYK2*) are important genes involved in this signalling cascade. The purpose of this work was to investigate the association and interaction of *IRF5, IRF7, TYK2* polymorphisms with SSc.