Background and Objectives B-cell activating factor of the TNF family (BAFF) is important for B cell maturation and plays a role in (auto)antibodies production. Elevated serum levels in relation to autoantibodies were documented in patients with IIM. Promoter region of BAFF gene contains several known sites with single nucleotide polymorphism (SNPs). An association between Rs9514828 (-871 C/T) SNP and susceptibility to idiopathic thrombocytopenic purpura was shown and possible relations to systemic lupus erythematosus, rheumatoid arthritis or Sjögren's syndrome were suggested but in IIM have not been studied yet. Here, we analysed relation of four BAFF SNPs located in the BAFF gene promoter with the development of IIM.

Materials and Methods 146 patients with polymyositis (PM), 150 with dermatomyositis (DM), 11 patients with juvenile DM and 4 patients with inclusion body myositis and 103 healthy individuals were included. Four SNPs located upstream in the BAFF gene (Rs9514827 (-2841 T/C); Rs3759467 (-2704 T/C); Rs1041569 (-2701 T/A); Rs9514828 (-871 C/T)) were analysed by direct DNA sequencing. Serum levels of BAFF (s-BAFF) were evaluated using ELISA. Autoantibodies were detected with immunoprecipitation. The chi square test for analysis of alleles and genotypes associations and SNPStats software for haplotype frequency studies were used.

Results Significantly higher frequency of -2701T allele was present in patients (18%) compared to healthy controls (12%) ($P = 0.029$; OR 1.684 (CI 95% = 1.050 – 2.699)). Additionally, increased -2841T allele ($P = 0.086$), -2841TT, CT genotype ($P = 0.066$) and -2701TT, AT genotype ($P = 0.079$) frequencies were observed in patients. SNPs were in strong linkage disequilibrium and formed four common haplotypes (TTAC, CTAT, TCAC, TTTT), with significantly different frequency ($>9\%$) distributions between patients and controls (global P -value < 0.038). Higher frequency of TTTT haplotype was present in patients (16.2%) compared to controls (9.3%; OR 1.99 (95% CI 1.15–3.47; $P < 0.015$)) relative to the most frequent haplotype TTAC. Significantly higher s-BAFF levels were detected in patients compared to healthy controls ($P < 0.0001$) and in patients with anti-Jo-1 or anti-PMscl autoantibodies compared to patients without autoantibodies ($P = 0.028$, $P < 0.037$ respectively). Higher s-BAFF levels with -2704T allele within anti-Jo-1+ patients ($P < 0.043$) were found.

Conclusions We describe significant association of SNP (Rs1041569) with myositis and a relation of SNP (Rs3759467) to presence of anti-Jo-1 autoantibodies and s-BAFF levels. These results should be confirmed in an independent cohort of patients and possible relations of s-BAFF levels with disease activity and treatment should be considered.

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A7.12 IDENTIFICATION OF THE SEMAPHORIN RECEPTOR PLEXIN-A2 AS A CANDIDATE GENE FOR SUSCEPTIBILITY TO ANKYLOSING SPONDYLITIS

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A Chatzikiyriakidou, PV Voulgari, AA Drosos. *Rheumatology Clinic, Department of Internal Medicine, Medical School, University of Ioannina, Greece*

Background and Objectives Semaphorins are a large family of secreted and membrane bound proteins linked to their receptors in a variety of cells and implicated with the development and function of many systems (nervous, immune, vascular) and organs (bone, heart, lung, kidney). Plexins and neuropilins are the primary semaphorin receptors. The present study addresses Plexin-A2 (PLXNA2) Rs6656560 variant in rheumatoid arthritis (RA), ankylosing spondylitis (AS), and psoriatic arthritis (PsA) susceptibility.

Materials and Methods One hundred thirty-six RA, 49 AS, 29 PsA patients and 147 controls were enrolled in the study. Polymerase

chain reaction coupled with restriction fragment length polymorphism analysis was used in Rs6656560 genotyping.

Results Statistical significant difference was observed in Rs6656560 genotypes' distribution between AS patients and controls ($P = 0.041$), but not between RA or PsA patients and controls ($P = 0.183$, $P = 0.729$; respectively). Similarly, significant difference was observed in Rs6656560 alleles' distribution between AS patients and controls ($P = 0.013$). Since AS and PsA both belong to spondyloarthropathies (SpAs), no statistical difference was observed in genotypes' distribution between these two groups ($P = 0.178$), while the statistical difference was significant between AS and RA patients ($P = 0.035$).

Conclusions The positive association of PLXNA2 polymorphism with AS susceptibility seems to indicate its effect in cellular semaphorin signalling related to bone development and remodelling, both of which are implicated in AS features. Additional studies are needed to ensure the revealed genetic association with AS predisposition and the effect of this variant in semaphorin/plexin complex function in specific cell types.

A7.13 IRAK1 RS3027898 POLYMORPHISM: A VARIANT IMPLICATED IN THE PATHOGENESIS OF MORE THAN ONE INFLAMMATORY DISEASE

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A Chatzikiyriakidou, PV Voulgari, AA Drosos. *Rheumatology Clinic, Department of Internal Medicine, Medical School, University of Ioannina, Greece*

Background and Objectives IRAK1 plays significant role in TLR dependent activation of the transcription factor NF- κ B, which subsequently increases the expression of many genes such as TNF- α and IL-8 related to immunological reactions. Polymorphism Rs3027898 located in the 3'-untranslated region of IRAK1 gene was studied for its association with rheumatoid arthritis (RA), psoriatic arthritis (PsA) and ankylosing spondylitis (AS) predisposition.

Materials and Methods The polymerase chain reaction-single strand conformation polymorphism analysis coupled with sequencing was used as the screening method for variant genotyping in 136 RA, 29 PsA, and 49 AS patients and 147 controls.

Results IRAK1 polymorphism Rs3027898 was revealed to be associated with all the studied inflammatory conditions. Specifically, strong statistically significant difference was observed in polymorphism distribution between RA patients and controls ($p = 0.044$), PsA patients and controls ($p < 0.001$), and AS patients and controls ($p < 0.001$). Grouping genotypes AA and AC versus CC the statistical difference was also significant in all groups: RA versus controls ($p = 0.017$), PsA versus controls ($p < 0.001$), and AS versus controls ($p = 0.010$).

Conclusions Here, we report IRAK1 gene polymorphism association with RA, PsA, and AS. This variant, previously, was also related to RA in patients with Chinese origin, with atherothrombotic cerebral infarction in Japanese patients, while we also revealed its association with ischemic stroke. In addition, another IRAK1 gene polymorphism (Rs1059703) was also related to atherothrombotic cerebral infarction, high CRP, chronic kidney disease, the induction of vaccine-induced immunity and sepsis outcomes but this variant did not differ significantly between our studied groups and controls (data not given). Taking into account that IRAK1 gene affects the activation of transcription factor NF- κ B, which is implicated in many immune related genes' expression, we could understand IRAK1 extensive association with many inflammatory conditions beyond patients' origin.

A7.14 IRF5 POLYMORPHISMS IN SYSTEMIC SCLEROSIS

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¹C Stock, ¹H Sato, ²C Fonseca, ¹AU Wells, ²CP Denton, ²DJ Abraham, ¹G Lindahl, ¹EA Renzoni. ¹Interstitial Lung Disease Unit, Royal Brompton Hospital, London, UK; ²Center for Rheumatology, Royal Free Hospital, London, UK

Introduction The transcription factor interferon regulatory factor 5 (IRF-5) plays a key role in the Toll-like receptor signalling pathway, and activation of the type I interferon response. As well as being associated with a number of other rheumatological diseases, including systemic lupus erythematosus and rheumatoid arthritis, *IRF5* has been identified as a candidate gene for systemic sclerosis (SSc) in a number of genome wide association studies. Although this finding has been replicated in several different studies, there has been variation in the single nucleotide polymorphisms (SNPs) tested, thereby making it difficult to determine which *IRF5* SNP(s) may be playing a role in susceptibility to SSc. We therefore tested a number of *IRF5* SNPs in a UK based population with the aim of elucidating the true causal variant(s).

Materials and Methods To investigate involvement of this gene in susceptibility to SSc, UK Caucasian patients and controls (SSc n = 465, controls n = 416) were genotyped using commercially available TaqMan assays. The *IRF5* SNPs Rs4728142, Rs2004640, Rs10954213, and Rs10488631, previously reported to be associated with SSc, were selected for investigation. The presence of pulmonary fibrosis was defined as a forced vital capacity <75% and/or the presence of fibrosis on chest imaging.

Results The allele frequencies of each of the four *IRF5* SNPs were not significantly different (using Bonferroni correction for multiple testing) in the healthy controls and patients with SSc (Rs4728142: 0.52/0.50, Rs2004640: 0.56/0.60, Rs10954213: 0.37/0.35, Rs10488631: 0.12/0.14). There was also no significant difference found for any of the SNPs when the SSc patients were subdivided according to disease type (limited/diffuse), presence of pulmonary fibrosis, or auto-antibody type.

Conclusions In contrast to previously published studies we did not detect a significant difference in allele frequency between patients with SSc and healthy control individuals for any of the four *IRF5* SNPs tested. However, due to the modest cohort sizes available, this study has limited power and therefore may have been unable to detect allele frequency differences with small effects. This study therefore will be repeated with larger cohorts in order to validate these results.

A7.15 LACK OF ASSOCIATION OF VARIANTS PREVIOUSLY ASSOCIATED WITH ANTI-TNF MEDICATION RESPONSE IN RHEUMATOID ARTHRITIS PATIENTS: RESULTS FROM A HOMOGENEOUS GREEK POPULATION

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¹MI Zervou, ²P Sidiropoulos, ¹E Myrthianou, ¹I Flouri, ³D Plant, ²P Rapsomaniki, ³A Barton, ^{4,5}DT Boumpas, ¹GN Goulielmos. ¹Laboratory of Molecular Medicine and Human Genetics, Medical School of Crete, Greece; ²Department of Rheumatology, Clinical Immunology and Allergy, University Hospital of Heraklion, Greece; ³Institute of Molecular Biology and Biotechnology, Foundation for Research and Technology, Heraklion, Greece; ⁴Medical School, University of Athens, Greece

Background Treatment strategies blocking tumour necrosis factor (anti-TNF) have proven very successful in patients with rheumatoid arthritis (RA), showing beneficial effects in about 50–60% of the patients. However, a significant subset of patients does not respond to the medication, for reasons that are still unknown.

Aim To validate five genetic factors, previously suggested to predict anti-TNF outcome, and two additional RA-associated SNPs in a cohort of anti-TNF-treated RA patients, from the homogeneous Greek island of Crete, Greece.

Materials and Methods The RA sample set consisted of 183 patients treated with the 3 anti-TNF biologic agents (Infliximab, Adalimumab and Etanercept) from the Clinic of Rheumatology of the University Hospital of Crete. Single Nucleotide Polymorphisms (SNPs) markers, namely *PTPRC* Rs10919563, *CD226* Rs763361, *AFF3* Rs10865035, *MyD88* Rs7744 and *CHUK* Rs11591741 SNPs were genotyped with Taqman primer-probe sets, while *TRAF1/CS*

Rs10818488 and *STAT4* *Rs7574865* genotyped following the Restriction Fragments Length Polymorphisms (RFLPs) approach. Odds ratios (OR) and 95% confidence intervals (CI) were calculated and the statistical difference in allele distribution was assessed by means of χ^2 test or Fisher's exact test.

Results We tested various demographic factors such as age, sex, and concomitant medications for correlation with treatment response to biologics. Disease activity score in 28 joints (DAS28) at baseline and after 6 months were available for these patients and analysis of good versus poor response at 6 months was performed for each SNP. In this cohort of patients, consisting predominantly of patients on infliximab (66.67%), none of the 7 successfully genotyped markers demonstrated association with treatment response.

Conclusions We conclude that the gene polymorphisms under investigation are not strongly predictive of anti-TNF response in RA patients from Crete (Greece). However, larger studies are needed to definitively exclude association of the SNPs under investigation in the Greek population and this study needs to be extended by involving more RA-associated SNPs in an attempt to predict anti-TNF outcome in Greece.

A7.16 LACK OF REPLICATION OF *PTPRC* GENE AS A PREDICTOR OF RESPONSE TO ANTI-TUMOUR NECROSIS FACTOR THERAPY IN PATIENTS WITH RHEUMATOID ARTHRITIS

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¹Helena Canhão, ¹Ana Rodrigues, ¹Maria Jose Santos, ¹Diana Carmona-Fernandes, ²José Costa, ³Helena Santos, ⁴Jaime Branco, ⁵Robert Plenge, ⁶Daniel Solomon, ⁶Jacome Armas, ⁷José António Silva, ¹João Eurico Fonseca, ⁵Elizabeth Karlson. ¹Rheumatology Research Unit, Instituto Medicina Molecular, Lisbon, Portugal; ²Rheumatology Department, Unidade Saúde Alto Minho, PonteLima, Portugal; ³Instituto Português Reumatologia, Lisbon, Portugal; ⁴CEDOC, Lisbon, Portugal; ⁵Division of Rheumatology, Brigham and Women's Hospital, Boston, USA; ⁶SEEBMO, Azores, Portugal; ⁷Rheumatology Department, Centro Hospitalar Universidade Coimbra, Coimbra, Portugal

Background and Objectives A genome wide association study (GWAS) with Caucasian Northern European and North American rheumatoid arthritis (RA) patients and a replication study with English patients, pointed out for an association between *PTPRC* locus and response to anti-TNF drugs in RA.

The Aim of our study was to evaluate whether this association is also verified in a population of Southern European (Portuguese) patients.

Materials and Methods We evaluated 383 RA patients from the Portuguese Rheumatic Diseases Register, Reuma.pt, for association between anti-TNF treatment response assessed by an absolute change in DAS28 at six months as the primary outcome and Rs10919563 *PTPRC* locus. We also studied the same association using the proportion of EULAR good responders and non responders at six months as the secondary outcome. Additive models were used taking the homozygote for the two major alleles as the reference variable.

Univariate and multivariate linear and logistic regression analyses were performed, adjusting for clinical variables that influenced treatment response.

Results Taking the continuous primary outcome, univariate and multivariate linear regression adjusted for DAS28 and HAQ at baseline showed no association between change in DAS28 at 6 months and *PTPRC* locus (p-values of 0.72 and 0.69 respectively). Also univariate and multivariate logistic regression (good versus non-responders) did not depict any association with this SNP.

Conclusions In this replication study with a cohort of RA. Portuguese patients, we did not observe an association between Rs10919563 *PTPRC* locus and response to anti-TNF treatment.