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 105 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.

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 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 (9.5%). 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 = 0.028, 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 IRAKI RS3027898 POLYMORPHISM: A VARIANT IMPlicated IN THE PATHOGENESIS OF MORE THAN ONE INFAMMatory DisEase


A Chatzikyriakidou, 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-kB, 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 156 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-kB, 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


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

Background and Objectives IRF5 is a transcription factor and crucial regulator of type I interferon (IFN) production, which is involved in immune activation and inflammatory disease development. Studies show that IRF5 polymorphisms are associated with several autoimmune and inflammatory diseases. We aimed to study the association of IRF5 polymorphisms with systemic sclerosis (SSc).

Materials and Methods We conducted a case-control study including 107 SSc patients (79 diffuse/9 limited cutaneous SSc) and 113 controls. Two single nucleotide polymorphisms (SNPs) were analyzed: IRF5 rs12029744 (Cytochrome P450 2C8, CYP2C8) and rs12029745 (Cytochrome P450 2C9, CYP2C9). Association of these polymorphisms with SSc was investigated using the chi-square test. The genotypic distribution was compared between patients and controls.

Results The frequency of the minor allele of IRF5 rs12029744 was significantly higher in SSc patients compared to controls (P = 0.005, OR = 2.79). No significant difference was observed for the IRF5 rs12029745 polymorphism between patients and controls (P = 0.57). A significant association between IRF5 rs12029744 and SSc was found in women (P = 0.03, OR = 3.66) but not in men (P = 0.17, OR = 1.43). The association was stronger in limited cutaneous SSc patients (P = 0.01, OR = 7.15) compared to diffuse cutaneous SSc patients (P = 0.07, OR = 2.51).

Conclusions Our findings suggest a potential role for IRF5 rs12029744 polymorphism in the susceptibility to SSc, particularly in limited cutaneous SSc patients. Further studies are needed to confirm these findings in larger cohorts and to investigate the mechanisms underlying this association.
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.

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

doi:10.1136/annrheumdis-2013-203221.16

1Helena Canhão, 1Ana Rodrigues, 1Maria Jose Santos, 1Diana Carmona-Fernandes, 2José Costa, 1Helena Santos, 3Jaime Branco, 2Robert Plenge, 2Daniel Solomon, 5Jacome Armas, 1José António Silva, 4 João Euroco Fonseca, 5 Elizabeth Karlson. 1Rheumatology Research Unit, Instituto Medicina Molecular, Lisbon, Portugal; 2Rheumatology Department, Unidade Saúde Alto Minho, PonteLima, Portugal; 3Institute Portugues Reumatologia, Lisbon, Portugal; 4CEDOC, Lisbon, Portugal; 5Division of Rheumatology, Brigham and Women’s Hospital, Boston, USA; 3SEEBMO, Azores, Portugal, 2Rheumatology 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 883 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.