Abstracts Accepted for Publication

Genomics, genetic basis of disease and HLA / T cell recognition

AB0001 FIRST DESCRIPTION AND FUNCTIONAL PROTEOMIC ANALYSIS OF A PROTECTIVE FOR RHEUMATOID ARTHRITIS GENE POLYMORPHISM

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Background: Rheumatoid Arthritis (RA) is the most common systemic autoimmune disease, with a respective expanded genetic research[1]. Immunogenetic studies have documented the positive correlation of various gene loci with incidence and/or disease profile. However, the description of gene loci negatively related to the incidence of RA is rarely documented. Apart from an early study involving HLA class II, there has been no reference to any genetic locus associated with a protective role against RA incidence.
Objectives: To identify the sequence of the functional areas of the TRAF1 (TNF receptor associated factor 1 - a protein involved in the intracellular signaling pathway of TNF) gene.
Methods: 172 patients and 95 controls were genetically assessed for the sequence of the seven exons of the gene TRAF1.
Results: On the position 9:120905076 of exon 7, the registered polymorphism G/A (rs143265058) was described in the controls group. The same polymorphism was not confirmed in any of the patients. Further functional proteomic study of the polymorphism with computing programs (software), revealed that the presence of this polymorphism leads to a differentiation of the quaternary structure of TRAF1 protein, possibly affecting the cohesion of intracellular TNF signaling pathway[2].
Conclusions: The present reference is one of the extremely rare genetic studies describing a protective gene locus against rheumatoid arthritis, and a pioneer of its kind in the use of Applied Informatics in the depiction of the quaternary structure of the encoded protein. At the same time, it is one of the few immunogenetic studies describing the functional proteomics of the encoded protein, plotting on a molecular level specific interaction modifications affecting the intracellular signaling pathway of TNF.
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Disclosure of Interest: None declared
DOI: 10.1136/annrheumdis-2017-eular.6818

AB0002 GENETIC STUDY OF THREE-PRIME REPAIR EXONUCLEASE (TREX1) IN THE SUSCEPTIBILITY TO SYSTEMIC LUPUS ERYTHEMATOSUS (SLE) AMONG EGYPTIAN PATIENTS

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Background: Interferon-alpha (IFNα) pathway has a crucial role in the pathogenesis of SLE. Many genes have been encoding with this pathway and their impaired expression have been reported in patients with SLE. *TREX1* is a DNA exonuclease involved in the metabolism and clearance of single stranded DNA from apoptotic cells, which is impaired in SLE[1]. *TREX1* mutations have been reported in SLE[2].
Objectives: Our study was aiming to assess the role of *TREX1* in the genetic susceptibility to systemic lupus erythematosus (SLE) among Egyptian patients.
Methods: Fifty SLE Egyptian patients and 50 age & sex matched healthy controls were included in this study. Based on the clinical history and immunological investigations, the 50 SLE patients were divided into two groups according to the presence of positive family history of autoimmune disease: Group I: 28 patients with positive family history & Group II: 22 patients with no family history. Further, the single exon of *TREX1* and its flanking sequences were amplified by PCR and sequenced in both directions.
Results: Our work showed a recurrent *TREX1* polymorphism rs11797 (c.531C>T) among Egyptian patients (56%) in comparison to control group (36%) (p value of 0.070) especially in cases with NPSLE, seizures and chilblains; with minor allele frequency of 0.28 in cases and 0.18 in controls (p value=0.342). *TREX1* polymorphism was present in 57.1% patients (16/28) of SLE patients in group I versus 54.5% patients (12/22) of SLE cases in, group II. The polymorphism was positively associated with neuropsychiatric manifestations (OR=7.000, 95% CI=0.791–61.975) and chilblains (OR=10.532, 95% CI=0.550–201.679). Furthermore, there was a statistically significant difference in cases with oral ulcers (p value=0.004), photosensitivity (p value=0.047) and seizures (p value=0.029).
Conclusions: We confirm that rs11797 (c.531C>T) could be associated with the susceptibility to neurological manifestations among the studied SLE patients.
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Disclosure of Interest: None declared
DOI: 10.1136/annrheumdis-2017-eular.2000

AB0003 A MIF PROMOTER POLYMORPHISM IS ASSOCIATED WITH THE SUSCEPTIBILITY TO PULMONARY ARTERIAL HYPERTENSION IN DIFFUSE CUTANEOUS SYSTEMIC SCLEROSIS PATIENTS

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Background: Systemic sclerosis (SSc) is a fibrotic immune-mediated disease of unknown etiology. Among its clinical manifestations, pulmonary involvement is the leading cause of mortality in SSc patients. However, the genetic factors involved in lung complication are not well-defined.
Objectives: We aimed to revisit the association of the MIF gene, which encodes a cytokine implicated in idiopathic pulmonary hypertension among other diseases, with the susceptibility and clinical expression of SSc, besides testing the association of this polymorphism with SScrelated pulmonary involvement.
Methods: A total of 4,393SSc patients and 16,591 unaffected controls from six cohorts of European origin were genotyped for the MIF promoter variant rs755622. An inverse variance method was used to meta-analyze the data.
Results: A statistically significant increase of the MIF rs755622*C allele frequency compared to controls was observed in the subgroups of patients with diffuse cutaneous SSc (dcSSc) and with pulmonary arterial hypertension (PAH) indepen-

dently (dcSSc: P=3.20E-2, OR=1.13; PAH: P=2.19E-02, OR=1.32). However, our data revealed a stronger effect size with the subset of SSc patients showing both clinical manifestations (dcSSc with PAH: P=6.91E-3, OR=2.05).
Conclusions: We revisited the association of the MIF rs755622*C allele with SSc and described a phenotype-specific association of this variant with the susceptibility to develop PAH in dSSc patients.
Disclosure of Interest: None declared
DOI: 10.1136/annrheumdis-2017-eular.1907

AB0004 PSORIATIC ARTHRITIS. GENES INVOLVED IN THE MESTIZO POPULATION

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Background: Psoriatic Arthritis (PsA) is not a regular systemic autoimmune disease, many expert define it with autoinflammatory disease, resulting in chronic inflammation of the synovium and consequent cartilage and bone erosion in approximately 10% of patients with skin psoriasis. It is important to identify novel genomic biomarkers associated with disease susceptibility but also able to detect early those patients with negative prognostic factors who may benefit from a more aggressive therapeutic approach. The over-expression of tumor necrosis factor (TNF)-a is a central element in the pathogenesis of psoriasis and psoriatic arthritis (2). The levels of TNF-alpha are under genetic control. An "A" at position *-308* in the *TNFA* promoter has been shown to be associated with increased level of TNF-alpha expression and "A" at position *-238* with a diminished level of TNF-α expression (3,4). Many authors consider that it is a disease only of Europeans descendants or Caucasians, however never be studied in mestizo population
Objectives: We investigate the potential association between the *TNFA*-238 G/A, *TNFA*-308 G/A, *IL10 -1082 G/A,-819C/T, -592C/A* polymorphisms and the Psoriatic Arthritis susceptibility.
Methods: The study included 52 PsA patients diagnosed by CASPAR criteria and 52 controls. The polymorphism of TNFA-308 G/A (rs1800629), TNFA-238 G/A (rs361525), IL10 -1082 G/A (rs1800896), -819C/T (rs1800871) and -592C/A (rs1800872) were genotyped by single specific primers -polymerase chain reaction (SSP-PCR). All subjects were from an unrelated Venezuelan-Mestizo population with a history of ancestors, at least back to the third generation
Results: When comparing allele and genotype frequencies between the groups studied, no significant differences were observed for the TNFA-308 G/A (rs1800629) and IL10 -1082 G/A (rs1800896), -819C/T (rs1800871) and -592C/A (rs1800872). However, our results showed a significant decrease in the frequency of the TNF-*238A* allele among PsA patients compared to healthy individuals (3.8% vs. 10.57%, respectively, OR: 0.31, 95% CI: 0.92 -1.05, p: 0.02), suggesting that *TNFA-238A* allele may have a protective effect (Table 1).

Table 1. Genotypic and allelic frequencies of the 308 G / AG (rs1800629) and -238 G / A (rs36152! variants of the TNFA gene in patients with psoriatic arthritis and healthy controls

TNFA-308 G/A (rs1800629)	PsA n=73	Controls n= 52	OR (IC95%)	*P*
Genotype				
GG	80,7%	84,6% (44)	0,76(0,27-2,12)	0,302
GA	19,3%	15,4% (8)	1,30(0,47-3,63)	0.302
AA	0%	0 % (0)		
Allele				
G	92,3%	90,4% (94)	1,27(0,48-3,37)	0,311
A	7,3 %	9,6% (10)	0,78(0,29-2,07)	0,311
TNFA-238 G/A (rs361525)	PsA n=73	Controls n= 52	OR (IC95%)	*P*
Genotype				
GG	92,3%	78,8% (41)	3,22(0,95-10,8)	*0,025
GA	7,7 %	21,2% (11)	0,31(0,09-1,05)	*0,025
AA	0	0		
Allele				
G	96,2%	89,4%(93)	2,95(0,91-9,61)	*0,0306
A	3,8%	10,6 %(11)	0,39(0,10-1,09)	*0,0306

NOTE: The values shown in parentheses represent the number of individuals carrying the genotype for the polymorphic site studied. The frequency is expressed as a percentage (p> 0.05: not significant, p <0.05: significant) psoriatic arthritis and healthy controls

Conclusions: This is the first genetic study carried out in Venezuelan mestizo patients with Psoriatic Arthritis to establish associations between genetic markers such as the polymorphisms of the promoter region of the TNFA and IL10 genes and the disease. In conclusion the *TNFA*-238 G/A polymorphism might play an important role in the development of Psoriatic Arthritis in Venezuelan mestizos and this association could not only clarify the different factors involved in a multifactorial disease, such as Psoriatic Arthritis, but also establish the relationship of these molecular markers with some clinical manifestations of the disease, which would allow in the future to determine the suitability or not to use some types of treatments, such as the use of anti-TNF therapy, for example.
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Acknowledgements: To bioanalyst Esther Guzmán, Marion DiMuro, Elena Flores and Mercedes Flores from the Clinica El Ávila and the University Hospital of Caracas (HUC/UCV), as well as Eva Salazar, Omar Balbas y Fernando Hernandez (IVIC).
Disclosure of Interest: L. A. Gutierrez-Gonzalez Grant/research support from: IIR/PFIZER, F. Herrera Grant/research support from: Grant Award (Pfizer), M. Fernandez Mestre: None declared
DOI: 10.1136/annrheumdis-2017-eular.1490

AB0005 CYTOKINE MRNA GENE EXPRESSION ASSOCIATED WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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Background: Systemic lupus erythematosus (SLE) is a complex polygenic autoimmune disease, characterized by autoantibody production, inflammatory manifestation and imbalanced cytokine production. In accordance with the pivotal role of Th17 cell in autoimmunity and the altered Th17/Tregs balance in response to changes in the cytokine milieu we analyzed mRNA expression of several cytokines in peripheral blood of SLE patients. Quantification of mRNA expression in peripheral blood could be useful to assess the disease activity of SLE patients.
Objectives: The aim of the present study was to investigate the gene expressions at mRNA level of proinflammatory (TNFA, IL18, IL12B); Th17-related (IL23A); immunosuppressive (TGFB1 and IL10) cytokines and Treg-specific transcription factor Foxp3 in peripheral blood of women with SLE.
Methods: Total RNA from peripheral blood was isolated from 28 female patients with SLE and 17 healthy women. Quantitative real-time polymerase chain reaction was performed for 7 genes of interests, using the TaqMan detection system. Relative quantitative evaluation of mRNAs was performed by the comparative ΔΔCt method and results are presented as n-fold mean difference (RQ-relative quantity) of target genes relative to calibrator (healthy controls) after normalization to the reference gene-GAPDH. Disease activity in SLE was determined by SLEDAI and divided into three categories: mild (0–5), moderate (6–10) and high (>10).
Results: The results reveal considerable overexpression of IL23A in SLE patients compared to healthy controls (RQ=5.347; $p<0.001$). According to the level of disease activity we found the highest elevation of IL23A in patients with SLEDAI>10 (RQ=8.54; $p<0.001$) compared to the controls. In inactive to mild (SLEDAI 0–5) and moderate SLE (SLEDAI 6–10), IL23A was also upregulated in approximately equal rate (RQ=4.976; $p<0.001$ and RQ=4.64; $p<0.001$). In addition, immunosuppressive cytokines IL10 and TGFB1 mRNA were elevated significantly in SLE patients than in controls (RQ=1.79; p=0.0077 and RQ=1.78; p=0.02, respectively). We also found that the expression of proinflammatory TNFA and IL12B were significantly downregulated approximately 2-fold. The mRNA level of Foxp3 was downregulated only for patients with SLEDAI>10. A significant good correlation between IL18 and the SLEDAI score was found (r=0.5548; p=0.002). Higher IL18 expression was observed among patients with worsened SLE compared to those with mild (RQ=1.656; p=0.008) and moderate (RQ=1.474; p=0.034) disease activity. We further demonstrated positively correlation between the expression levels of IL23A and TGFB1 (r=0.7276; $p<0.001$) among SLE patients.
Conclusions: These results suggest that upregulation of IL23 and TGFB1 in addition to downregulated Foxp3 expression may contribute to skewing towards Th17 profile in SLE pathogenesis and this was the most markedly manifested at the highest level of disease activity. Our results support indirectly the idea for restoring Th17/Treg balance as a therapeutic target in SLE.
Disclosure of Interest: None declared
DOI: 10.1136/annrheumdis-2017-eular.2299

AB0006 MICRORNA-499 IN BEHCET DISEASE AND POSSIBLE ASSOCIATION WITH DISEASE ACTIVITY

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Background: Behçet Disease (BD) is a relapsing inflammatory autoimmune disease. Although the etiology of BD is not yet known, genetic predisposition and immune dysregulation are thought to be critical factors in the pathogenesis of the disease. MicroRNAs (miRNAs) are small RNA fragments that can regulate the gene expression. miRNAs play a critical role in the pathogenesis of autoimmune or auto inflammatory diseases. Sinngle nucleotide polymorphisms (SNPs) may change the property of miRNAs through altering miRNA expression and/or maturation.
Objectives: The aim of this work was to detect miRNA-499 (rs3746444) genotyping and relative expression in BD patients in order to find out the possible association between them and disease activity and severity.
Methods: Relative expression of miRNA-499 was measured by Real-Time PCR and miRNA-499 gene (rs 3746444) genotyping was performed by TaqMan SNP