Figure 1: (A) Heatmap of DEGs: The red and blue colors represent up-regulation and down-regulation, respectively. (B) Volcano map of gene expression: The horizontal axis is $\log_2 FC$, the vertical axis is $\log_{10} \text{adj. P.Val}$. Each dot represents a gene, blue indicates low expression genes, red indicates high. (C, D, E, F) Visualization GO enrichment analysis and KEGG pathway enrichment analysis. (G, H) PPI network and hub gene identification: Top 9 hub genes in the PPI network were screened by Cytoscape plugin Cytoscape based on their degree value (high degree value) to yellow (low degree value).

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AB0006 GENETIC RISK PROFILE FOR PSORIATIC ARTHRITIS PREDISPOSITION IN ITALIAN PATIENTS

M. S. Chimenti¹, C. Ciccacci², G. De Benedittis³, A. Latini³, P. Conigliaro¹, G. L. Fonti¹, P. Triggianese¹, P. Borgiani³, R. Perricone¹. ¹University of Rome Tor Vergata, Rheumatology, Allergy and Clinical Immunology, Rome, Italy; ²UniCamillus - Saint Camillus International University of Health Sciences, Genetics Unit, Rome, Italy; ³University of Rome Tor Vergata, Genetics Unit, Rome, Italy

Background: Psoriatic arthritis (PsA) is a chronic inflammatory joint disease typically associated with psoriasis and classified in the group of spondyloarthritis (1). The pathogenesis is based on an interplay of different genes interacting with several environmental factors including stress, trauma, infections, triggering an inflammatory response related to the activation of innate and acquired immunity in different tissues and organs (2). However, the risk for the development of PsA is not clearly understood.

Objectives: The aim of this study was to evaluate, in a cohort of Italian PsA out-patients of the Rheumatology Unit of the University of Rome Tor Vergata, the association of genetic variants in candidate genes for PSA susceptibility and their possible contribute in the modulation of clinical and laboratory features.

Methods: The genes were selected according to previous studies describing these genes as involved in susceptibility to rheumatoid arthritis (RA) (3), since

a common genetic background can be shared between these diseases. Nine SNPs (single nucleotide polymorphism) in eight candidate genes were analysed: STAT4 (rs7574865), TRAF3IP2 (rs33980500), TNFAIP3 (rs6920220 and rs2230926), MIR146A (rs2910164), PSORS1C1 (rs2233945), IL-10 (rs1800872), HCP5 (rs3099844) and ERAP1 (rs27524). Polymorphisms were analysed in 163 consecutive PsA out-patients and 198 healthy controls (HC). Genotyping was performed by allelic discrimination by TaqMan assay. Alleles frequencies differences between cases and controls or between phenotypic groups were compared using Pearson's χ^2 test.

Results: We have observed an association between PSA susceptibility and the variant alleles of STAT4 [OR= 1.60 (1.15-2.21), P= 0.005], TRAF3IP2 [OR= 1.65 (1.01-2.65), P= 0.04], ERAP1 [OR= 1.40 (1.05-1.85), P= 0.02] and TNFAIP3 (rs6920220) [OR= 1.75 (1.19-2.57), P= 0.004]. On the contrary, the variant allele of IL-10 polymorphism seems to play a protective role [OR= 0.74 (1.05-1.85), P= 0.05]. Moreover, in order to define a genetic risk profile, we have counted the total number of risk alleles in each subject, considering as risk alleles the allelic variant of rs7574865 (STAT4), rs33980500 (TRAF3IP2), rs6920220 (TNFAIP3) and rs27524 (ERAP1) SNPs. Then, we have compared the risk allele number distribution between patients and HC (Fig.1). Classes with 3 or more risk alleles are significantly more represented in patients than in HC (OR= 2.03, P=0.004). The risk to develop the disease increases significantly in subjects with at least four risk alleles (OR= 2.96, P=0.002).

Figure 1. Number of risk alleles in patients and controls: rs7574865 (STAT4), rs33980500 (TRAF3IP2), rs6920220 (TNFAIP3) and rs27524 (ERAP1) SNPs.

Conclusion: We confirm the associations between five SNPs, already studied in RA, and PSA susceptibility, suggesting a common inflammatory pathway in chronic inflammatory rheumatological diseases. Moreover, we show how the genotyping of only few associated SNPs could help to define a genetic risk profile for PSA development.

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AB0007 STAT4 RS7574865 G/T POLYMORPHISM AS MARKER OF PREDISPOSITION TO SYSTEMIC LUPUS ERYTHEMATOSUS WITH JUVENILE ONSET

M. Kaleda¹, M. Krylov², I. Nikishina¹. ¹V.A. Nasonova Research Institute of Rheumatology, Pediatric Department, Moscow, Russian Federation; ²V.A. Nasonova Research Institute of Rheumatology, Genetic Department, Moscow, Russian Federation

Background: Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with a significant genetic predisposition. Recent studies have identified STAT4 (signal transducers and transcription activators 4) as a susceptibility gene for SLE.

Objectives: To investigate the hypothesis of the association of STAT4 rs7574865 G/T polymorphism with the predisposition to SLE in children and its relationship with some of SLE manifestations.

Methods: The case-control pilot study included 143 children (39 with SLE and 103 healthy unrelated volunteers as a control group). Diagnosis of SLE was based on 2012 SLICC criteria. STAT4 rs7574865 G/T polymorphism was investigated using allele-specific real-time polymerase chain reaction (RT-PCR).

Results: The group of pts with SLE consisted of 29 girls and 10 boys, with an average age of 11.8±3.7 years (from 3 to 17 years) and an average disease duration of 4.1±2.4 years. 79.5% pts had acute cutaneous lupus at the onset, 46.1% - non-scarring alopecia, 71.8% - arthritis, 23.1% - oral and nasal ulcers, 23.1% - serositis, 43.6% - renal involvement, 35.9% - neuropsychiatric disorders. Leucopenia/lymphopenia was found in 71.8% of pts, thrombocytopenia - in 23.1%. ANA were detected in 100% pts, anti-dsDNA - in 79.5%, anti-Sm - in 31.6%, antiphospholipid antibodies - in 7.3%, hypocomplementemia - in 61.5%, positive direct Coombs test - in 35.9%. Macrocephalic activation syndrome at the onset was documented in 15.4 % of pts. The distribution of rs7574865 genotypes in the control group showed no significant deviations from the Hardy-Weinberg equilibrium. The distribution of genotype frequencies among pts had statistically significant differences compared to the control ($\chi^2=12.95$, $p=0.0015$): GG-30.8% and 63.1% ($p=0.001$), GT-56.4% and 33.0% ($p=0.018$), TT-12.8% and 3.9% ($p=0.114$), GT+TT - 69.2% and 36.9% ($p=0.0005$). The frequency of the mutant STAT 4 allele T (polymorphism), was significantly higher in the SLE group than in the control group (41% and 20.4%, respectively; $p=0.0007$). We identified an association of the T allele with some clinical, laboratory, and immunological disorders in SLE: arthritis (OR 3.9, $p=0.0002$), acute cutaneous lupus (OR 2.47, $p=0.003$), non-scarring alopecia (OR 3.12, $p=0.002$), renal involvement (OR 2.42, $p=0.022$), leucopenia (OR 2.72, $p=0.003$), thrombocytopenia (OR 4.88, $p=0.002$), anti-dsDNA (OR 2.82, $p=0.0006$), hypocomplementemia (OR 2.34, $p=0.012$), positive direct Coombs test (OR 3.38, $p=0.002$).

Conclusion: Our pilot study confirmed that the STAT4 rs7574865 G/T polymorphism was associated with the risk of SLE in children and some of SLE manifestations.

Disclosure of Interests: None declared

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AB0008

APPLYING WHOLE EXOME SEQUENCING TO FAMILIAL ANTIPHOSPHOLIPID SYNDROME: NEW PLAYERS IN A RARE DISEASE?

A. Barinotti¹, M. Radin¹, I. Cecchi¹, S. G. Foddai¹, E. Rubini¹, D. Roccatello¹, S. Sciascia¹, E. Menegatti¹. ¹University of Turin, Clinical and Biological Sciences, Turin, Italy

Background: Antiphospholipid Syndrome (APS) is an autoimmune disease whose precise aetiology is still unknown, but the high heterogeneity of its manifestations and clinical course is presumably due to the occurrence of different mechanisms and alterations at different levels and pathways [1]. The first genetic studies in APS focused primarily on the human leukocytes antigen system region, but more recent data highlighted a role of other genes in APS susceptibility, primarily those involved in the immune response and in the haemostatic process.

Objectives: We aimed to deepen the investigation of APS genetic background starting from a case of familial APS, analysing two siblings with thrombotic APS (Table 1), both triple positive for antiphospholipid antibodies (aPL).

Table 1. Main clinical and laboratory characteristics of the patients included in the study.

Patient	Age	aPL Profile	Relevant Clinical History
1 (F)	51	Triple positive (LA, aCL IgG, aβ2GPI IgG)	Two episodes of ischemic stroke, one episode of CAPS (renal thrombotic microangiopathy, visual impairment, ischemic stroke)
2 (M)	47	Triple positive (LA, aCL IgG, aβ2GPI IgG)	Three episodes of deep vein thrombosis, regardless ongoing well conducted therapy vitamin k antagonist and additional retinal vein thrombosis

LA: lupus anticoagulant; aCL: anti-cardiolipin antibodies; aβ2GPI: anti- β2 glycoprotein I antibodies; CAPS: catastrophic APS.

Methods: Genomic DNA was extracted from peripheral blood and the samples underwent Whole Exome Sequencing (WES). Sequencing was done on a 100X coverage, and reads have been aligned to the human reference genome (GRCh37/hg19 assembly) using the Burrows-Wheeler Alignment tool (BWA). The mean sequencing depth on target regions was 170X for patient 1, 205X for patient 2, moreover, 99.50% of the targeted bases had at least 10X coverage for all the three donors. The resulting single nucleotide polymorphisms (SNPs) have been analysed through a step-by-step process based on their frequency population (using Genome Aggregation Database), their predicted effects on the protein (using VarSome) and a literature research about the genes carrying them. Moreover, genes previously associated with a pro-thrombotic tendency and with APS have been analysed in the two patients.

Results: Starting from more than 120000 SNPs for each patients, the analysis led to reduce the list of SNPs of interest to 27 missense mutations. The complete literature research regarding the genes carrying these mutations allowed to further reduce the number of selected genes, focusing on those that exert a role potentially involved in APS pathogenesis and development. In particular, these genes (*PLA2G6*, *HSPG2*, *BCL3*, *ZFAT*, *ATP2B2*, *CRTC3* and *ADCY3*) take part in the immune response and the vascular homeostasis. The list of the DNA missense variants of interest found in our cases of familial APS is resumed in Figure 2.

GENE	FULL NAME	SNP	CHR	COORDINATE	TRANSCRIPT	VARIANT EFFECT
CROCC	Clary novel coiled-coil domain	c1144279934 (A/T)	1	17238697	NSM 014075.1	Missense variant (p. Glu234Ala)
HSPG2	Heparan sulfate proteoglycan 2	c276663773 (C/T)	1	22207915	NSM 005528.5	Missense variant (p. Arg570His)
KIF14	Kinesin family member 14	c331895990 (C/T)	1	20593037	NSM 014375.2	Missense variant (p. Arg190Gln)
ADCY3	Adenylyl cyclase 3	c584083662 (C/T)	2	25606928	NSM 004063.3	Missense variant (p. Val789Met)
CR3P1	Chlamydomonas reinhardtii receptor 1	c1140137679 (A/C)	3	934319	NSM 014343.2	Missense variant (p. Tyr107Phe)
SRGAP3	SLIT-ROBO Rho GTPase activating protein 3	c762133718 (C/T)	3	914644	NSM 014350.3	Missense variant (p. Arg130Gln)
ATP2B2	A P2-type plasma membrane Ca ²⁺ transporting 2	c581257856 (G/A)	3	10382352	NSM 00101331.2	Missense variant (p. Ala385Val)
OSXND1	Oxidoreductase NAD binding domain containing 1	c1140137679 (A/C)	3	16343175	NSM 130317.1	Missense variant (p. Phe139Gln)
PDZD2	PDZ domain containing 2	c1140137679 (A/C)	5	22097311	NSM 176140.2	Missense variant (p. Pro2737Asp)
FAT2	FAT atypical cadherin 2	c762133718 (C/T)	5	150915618	NSM 001447.2	Missense variant (p. Arg495Gln)
ORF1	Orf1 domain containing 1	c777034277 (T/C)	7	114367370	NSM 012369.2	Missense variant (p. Phe103Leu)
ZFAT	Zinc finger and AT hook domain containing	c584083662 (C/T)	8	135894714	NSM 020663.2	Missense variant (p. Arg390Cys)
ITIH3	Interleukin-1 type 3	c338347	9	21229335	NSM 021258.2	Missense variant (p. Tyr119Ile)
ZNF462	Zinc finger protein 462	c326A/T	9	10966419	NSM 021254.4	Missense variant (p. Asn757Ile)
MRPL48	Mitochondrial ribosomal protein L48	c743995790 (G/T)	11	73555903	NSM 016055.5	Missense variant (p. Asn475Val)
LYBP2	Lysine binding protein 2	c1140137679 (A/C)	14	9499123	NSM 000428.2	Missense variant (p. Asp74Glu)
CRTC3	CRTC3 regulated transcription coactivator 3	c168C/T	15	91083301	NSM 022508.4	Missense variant (p. Leu555Phe)
USP32	Ubiquitin specific peptidase 32	c1140137679 (A/C)	17	58311560	NSM 025282.3	Missense variant (p. Leu390Pro)
BNIP2	Birc2 domain containing 2	c1140137679 (A/C)	18	12009990	NSM 014214.2	Missense variant (p. Val103Asn)
MYC16	Myosin 16	c2609295232 (C/T)	19	96057604	NSM 025096.2	Missense variant (p. Glu453Gln)
CC2D4A	Coiled-coil and C2 domain containing 1A	c794G/T	19	11028928	NSM 017721.4	Missense variant (p. Arg265Asn)
MAP3K10	MAP kinase kinase kinase 10	c338G/A	19	46098296	NSM 002446.3	Missense variant (p. Glu120Lys)
BCL3	BCL2 transcription coactivator	c747455406 (C/A)	19	45262863	NSM 004918.4	Missense variant (p. Met181Asn)
MRMR	Mitochondrial ribosomal maintenance 8 homologous recombination repair factor	c768426146 (G/A)	20	5933350	NSM 00121521.1	Missense variant (p. Arg511Ile)
PLA2G6	Phospholipase A2 group VI	c780423461 (C/G)	22	38528920	NSM 003568.2	Missense variant (p. Cys332Ser)

Figure 2. List of DNA missense variants of interest found in patient 1 and 2. Genes potentially involved in APS pathogenesis and development are highlighted in bold.

No mutations on genes known to be associated with a pro-thrombotic state (*F5*, *F2*, *MTHFR*, *F13A1*, *PROC*, *PROS1*, *FGB* and *SERPINE1*), or on genes previously associated with APS (*B2GPI*, *PF4V1*, *SELP*, *TLR2*, *TLR4*, *GP Ia*, *GP1BA*, *F2R*, *F2RL1*, *TFPI*, *F3*, *VEGFA*, *FLT1*, and *TNF*) have been found in the WES analysis.

Conclusion: To some extent, this can be seen as a proof of concept of the complexity of APS. Efforts to interpret the genetic risk factors involved in the heterogeneous clinical features of the syndrome, for instance, the integration of WES and network-based approaches might help to identify and stratify patients at risk of developing APS.

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AB0009

ASSOCIATION OF STAT4 RS7574865, RUNX1 RS9979383, IL6 RS1800795, IL6R RS2228145, IL6R RS4845618 WITH SYSTEMIC LUPUS ERYTHEMATOSUS SUSCEPTIBILITY AND SOME LUPUS MANIFESTATIONS IN BELARUSIAN POPULATION

N. Dostanko¹, V. Yagur¹, R. Goncharova², E. Siniauskaya², T. Zyalova¹.

¹Belarusian State Medical University, 2-nd Department of Internal Medicine, Minsk, Belarus; ²National Academy of Sciences of Belarus, Institute of Genetics and Cytology, Minsk, Belarus

Background: Systemic lupus erythematosus (SLE) has a significant genetic predisposition. Many genetic variants of susceptibility to SLE have been published and analyzed, but the clinical and functional significance of the various genotypes has not yet been clearly defined [1].

Objectives: To estimate the association between some of non-HLA gene polymorphisms such as STAT4 rs7574865, RUNX1 rs9979383, IL6 rs1800795, IL6R rs2228145, IL6R rs4845618 and susceptibility to SLE in Belarusian population as well as some disease manifestations.

Methods: We examined 383 healthy blood donors and 54 SLE patients (18-72 years old, median age 35) classified according to the 1997 American College of Rheumatology (ACR) revised classification criteria [2]. Deoxyribonucleic acid was extracted from peripheral blood samples by phenol-chloroform method. Genotyping was performed by real-time PCR with fluorescent probes. Differences of distribution of all the single nucleotide polymorphism (SNP) genotypes and their associations with secondary antiphospholipid syndrome (APS) and lupus arthritis were analyzed using Pearson χ^2 (χ^2) and two-way Fisher exact test ($F_{p,2}$). Diagnostic odds ratio (dOR), likelihood ratio of positive (LR⁺) and negative (LR⁻) tests and corresponding 95% confidence intervals (CI) were also calculated.

Results: We revealed significant difference in STAT4 rs7574865 genotypes in SLE patients and healthy donors ($\chi^2=8.27$, $p=0.016$) with significant increase of TT genotype frequency in SLE patients vs healthy donors ($\chi^2=6.83$, $p=0.009$; $p_{2-1}=0.020$; dOR=3.78 (CI_{95%} 1.36-10.55); LR⁺=3.44 (CI_{95%} 1.35-8.71); LR⁻=0.91