Genetic evaluation of molecular traits in systemic lupus erythematosus

S09.3 CHANGES IN THE CAUSES AND PREDICTORS OF LUPUS MORTALITY IN SPAIN THROUGH THE LAST DECADES: DATA FROM THE RELESSER REGISTRY

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10.1136/lupus-2022-elm2022.18

Purpose To analyze the causes and identify predictive factors of mortality of Systemic Lupus Erythematosus (SLE), and to assess the time evolution and chronological changes in Spain.
Methods We performed a cross-sectional and retrospective study analyzing data from the RELESSER cohort (Spanish Registry of SLE of the Spanish Society of Rheumatology). Sociodemographic, clinical and serological variables, comorbidities and treatments, as well as indicators of disease activity, damage and severity were recorded. We excluded patients with lost information about the death variable and analyzed the differential features of deceased patients in comparisons with survivors through different time stages according to the date of diagnosis: until the 1980's; the 1990's and the first decade of the 21st century. Variables associated with mortality in univariate analysis were entered into different multivariate models to determine which ones were independently associated with the outcome of the disease in each decade.
Results A total of 3665 patients were included, mostly caucasian female with similar general features regardless of the different time stages analyzed. The 18.4% until the 1980's, the 5.97% in the 1990's and up to 2.84% of the individuals in the first decade of the 21st century, had died. The main age of death was similar in the different groups, around 55-58 years old (Table). The vascular events were the leading cause of death until the 1980's, while in the last two decades, were SLE activity followed by infections.

The older age at diagnosis was predictor of mortality in our cohort. Neither gender nor delay in diagnosis was independently associated with mortality, with the exception of the female sex, which behaved as a protective factor until the 1980's.

The mortality predictors in our cohort were the presence of hypocomplementemia, organ damage, ischemic disease and hospitalizations until the 1980's; thrombocytopenia, thrombosis, antiphospholipid syndrome and valve disease in the 1990's; nephritis, organ damage, depression, severe infections and ischemic disease in the first decade of the 21st century. Conversely, skin involvement was related to greater survival over the last two decades of the study.

The use of high doses of corticosteroids was predictor of mortality in each time stage, as well as the use of cyclophosphamide and rituximab from the year 2000. Antimalarial treatment was linked to improved survival in all the decades analyzed as well as the use of mycophenolate in the 1990's.
Conclusions In the RELESSER cohort, the main causes of death were disease activity and infections, with the exception until the 1980's, which were vascular events.

The older age at diagnosis, the use of corticosteroids and comorbidities, were associated with a significant increase in mortality in SLE, while antimalarial treatment was linked to improved survival. Data indicate that organ damage is a risk factor and skin involvement is a protective factor against mortality. Differentially, female sex until the 1980's was independently associated to improved survival, and depression at the beginning of the 21st century was linked to mortality.

Thursday 06 October 2022 from 10:20 to 11:50

S10 GENETICS IN SLE

S10.1 GENETIC EVALUATION OF MOLECULAR TRAITS IN SYSTEMIC LUPUS ERYTHEMATOSUS

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10.1136/lupus-2022-elm2022.19

Purpose Systemic Lupus Erythemathosus (SLE) is a prototypic systemic autoimmune disease characterized by a complex aetiology. Epigenetic alterations are known to be mediators of the environmental and genetic factors and to impact transcriptional programs. Here we aim to investigate genetic correlations between SLE and different molecular traits such as DNA methylation, gene expression and protein level by computing genotypic risk scores for the intermediate traits.
Methods We use genotypes for 13,482 European ancestry individuals obtained from pre-existing projects studying SLE genetics, i) 4,174 SLE patients from a collection of SLE cohorts and 4,048 healthy controls from the University of Michigan Health and Retirement Study, ii) 696 SLE patients and 304 healthy controls from the International Consortium for Systemic Lupus Erythematosus Genetics and iii) 397 SLE patients and 561 healthy controls from the PRECISESADS Consortium. We computed genotypic risk scores for biomarkers using the GENOSCORES platform and tested the association between scores and the SLE phenotype using a logistic regression model for each score separately and adjusting for sex and 20 genetic principal components.
Results We computed 1,716 locus-specific genotypic scores for loci affecting human plasma proteins (pQTLs). We detected 7 protein scores significantly associated with the SLE phenotype at Bonferroni correction. One of the 7 proteins, FCGR2B, is already known in SLE pathogenesis. Additionally, 4 protein scores were located within the HLA region in chromosome 6 (AMBN, ATF6, EDA, FIBCD1) and the remaining 2 (AXIN2, TREML4) scores were located in chromosome 14. Furthermore, we computed scores for the gene expression of these 7 proteins in different tissues and showed that scores for the gene expression of the AXIN2 gene were significantly associated with the SLE phenotype.
Conclusions and Ongoing Analyses This study expands the list of candidate proteins associated with SLE and regions that might contain novel genes implicated in the SLE phenotype. Our findings demonstrate how genotypic scores for molecular traits can be used to identify and characterize genetic associations with complex disease traits. We aim to further explore

the detected associations by considering DNA methylation traits and their association with SLE.

S10.2 INTERACTION BETWEEN HLA-DRB1*03:01 AND STAT4 IS ASSOCIATED WITH INCREASED RISK OF NEPHRITIS IN SYSTEMIC LUPUS ERYTHEMATOSUS

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10.1136/lupus-2022-elm2022.20

Purpose Lupus nephritis (LN) is a major cause of morbidity in Systemic Lupus Erythematosus (SLE) and a subset of patients still develop end stage renal disease (ESRD). Genetics is important in SLE pathogenesis and today >180 SLE risk loci have been identified at Genome-wide significance (GWS). Here we investigate how gene-gene interactions influence the risk of WHO class III or IV LN in patients with SLE.

Methods Patients with SLE from Sweden and Norway (n=1455) were genotyped with Illumina's Global Screening Array. Clinical information was retrieved from medical charts, including kidney biopsy data classified according to the WHO. Eleven SLE GWS risk single nucleotide polymorphisms (SNPs) were analyzed regarding gene-gene interaction for LN; ITGAM, IRF5, STAT4, IL12A, TYK2, PTPN22, TNFSF4, BANK1, BLK, and two tag SNPs for HLA-DRB1*03:01 and HLA-DRB1*15:01. Data was analyzed using cox regression and logistic regression including the individual SNPs, sex and SLE duration as covariates (SPSS version 28.0.1.0 (142)). P-value < 0.05 was considered significant.

Results In total, 33% (476/1455) of patients had a history of LN, according to the ACR-82 criteria, with an average age at onset of 33 years. Kidney biopsy data was available for 301 patients and 65% (197/301) of the biopsies showed WHO class III or IV LN. Comparing patients with class III/IV LN with non-nephritis patients, we identified a significant interaction between the HLA-DRB1*03:01 and STAT4 risk alleles (OR 3.4 (1.4–8.3), p= 0.009 for 3 risk variants and OR 9.1 (1.1–73), p= 0.037 for 4 risk variants), Table 1. An interaction was also observed when including patients with 3 or 4 risk variants as one group in a model (OR 3.3 (1.4–8.0), p= 0.008). The prevalence of class III/IV LN in patients with 3–4 risk variants was 30% (24/81) compared with 16% (166/1059) in patients with 0–2 risk variants, p = 0.001. Furthermore, patients with 3–4 risk alleles displayed a decreased time from SLE diagnosis to the onset of class III/IV LN (HR 2.6 (1.1–5.8), p= 0.022) compared with patients with 0–2 risk alleles. Finally, when analyzing the 2 SNPs separately for association with class III/IV LN, no association was observed for STAT4, but patients homozygous for the HLA-DRB1*03:01 tag risk allele had an increased risk (OR 1.9 (1.0–3.5), p= 0.036).

Conclusions An interaction between HLA-DRB1*03:01 and STAT4 risk gene variants increase the risk of WHO class III and IV LN in SLE. The results indicate an importance of gene-gene interaction for LN development and a potential role of interactions between genes in SLE pathogenesis.

Abstract S10.2 Table 1 Logistic regression. WHO class III/IV nephritis vs. non-nephritis

	OR (CI 95%)	P-value
Covariates: gender, disease duration, a HLA-DRB1*03:01 tag SNP[a] and *STAT4*[b]		
HLA-DRB1*03:01 × *STAT4*		
1[c]	1.1(0.6-2.3)	0.726
2[c]	**3.4(1.4-8.3)**	**0.009**
4[c]	**9.1(1.1-73)**	**0.037**

[a]rs1269852(C), [b]rs11889341(T), [c] interaction term

S10.3 GENETICAL AND PHENOTYPICAL FINDINGS OF CHILDHOOD-ONSET SYSTEMIC LUPUS ERYTHEMATOSUS

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10.1136/lupus-2022-elm2022.21

Purpose to identify the presence of variants in gene related to monogenic lupus and their relationship with clinical manifestations in childhood-onset systemic lupus erythematosus (cSLE) or lupus-like phenotype.

Methods a descriptive, observational, cross-sectional study was carried out in children with a diagnosis of cSLE or with lupus-like. The genetic analysis (Sanger/Clinical Exome Sequencing) was performed from isolated DNA obtained from blood sample.

Results Forty-two children were included in the study. The genetic analysis detected at least one variant in 11 (26.1%) children, 5 (45.4%) with cSLE and 6 (54.5%) with lupus-like phenotype. Of those who carry a genetic variant, the median age at disease onset was 11 years (range: 2–16) and 72.7% were female. Most of them were Caucasians (72.7%). Four (36.3%) and 3 (27.2%) out of 11 patients had a positive family history and/or a personal history for autoimmune diseases, respectively.

Regarding the clinical manifestations at onset, musculoskeletal was the most frequent (8 patients, 72.7%), followed by hematological (6 patients, 54.5%), cutaneous (6 patients, 54.5%), constitutional with fever (5 patients, 45.45%), neurological (4 patients, 36.3%), renal (3 patients, 27.2%), cardiac (3 patients, 27.2%) and pulmonary (2 patients, 18.1%) manifestations.

Related to immunological parameters, 10 (90.9%) were ANA positive, 5 (45.4%) anti-dsDNA, 4 (36.3%) ENA and 2 (18.1%) were antiphospholipid antibodies and lupus anticoagulant positive. Both C3 and C4 were low in 5 (45.4%) children and isolated C3 levels were low in 4 (36.3%) patients.

Among the variants, we found that only two patients who carry a TREX variant showed normal C3 and C4 levels; one of them presented with lupus pernio as reported in literature. The same RNASEH2B (c.868G>A) variant was identified in two siblings with similar phenotype. The patient who carried the SHOC2 variant presented polyarthritis and serositis, while the patient with the TNFRSF13B variant onset with a glomerulonephritis. Those manifestations have already been described related to these gene variants. Clinical manifestations and variants are detailed in Table 1.