

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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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.

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

Covariates: gender, disease duration, a HLA-DRB1*03:01 tag SNP ^a and STAT4 ^b	OR (CI 95%)	P-value
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

^ars1269852(C), ^brs11889341(T), ^c interaction term

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.

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

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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.