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. 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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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.

Abstract S10.3 Table 1 Gene variants, clinical and immunological features. aB2GP, anti-B2glycoprotein; aCL, anti-cardiolipin; ANA, antinuclear antibodies; APL, antiphospholipid antibodies; ENA, F, female; GG, adenopathy; GMN, glomerulonephritis; ILD, interstitial lung disease; LA, lupus anticoagulant; M, male; MAS, macrophagic activation syndrome; LN, lupus nephritis; SLE, systemic lupus erythematosus; TTP, thrombotic thrombocytopenic purpura; WMI, whiter matter hyperintensities. Highlighted in yellow, are shown the manifestations which have already been described in the literature related to the gene variant

Gene variant	Diagnosis	Gender	Age at disease onset (years)	Cutaneous manifestations N=6 (54.5%)	Musculoskeletal manifestations N=8 (72.7%)	Hematological manifestations N=6 (54.5%)	Fever N=5 (45.4%)	Pulmonary manifestations N=2 (18.1%)	Cardiac manifestations N=3 (27.2%)	Neurological manifestations N=4 (36.3%)	Renal manifestations N=3 (27.2%)	Other manifestations N= 2 (18.1%)	C3/C4 N=9 (81.8%)	ANA N=10 (90.9%)	DNA N=5 (45.4%)	ENA N=4 (36.3%)	APL N=2 (18.1%)
ADAR c.16-8 T>C	SLE	F	11	No	Arthralgia	Anaemia, lymphopenia, neutropenia	Yes	No	No	No	No	Ascites, intestinal vasculitis, lupus hepatitis	Low/ Low	1:80	1:40	RNP+	Neg
TNFAIP3 c.2170A>C	SLE	F	16	Rash	No	Anaemia, lymphopenia, neutropenia	Yes	No	Conduction disorder	No	LN	No	Low/ Low	1:2560	1:320	Neg	Neg
RNASEH2B c.105 107delAAT	SLE	F	5	No	Arthralgia	Thrombocytopenia, leukopenia	No	No	Serositis	No	No	No	Low/ Normal	1:320	Neg	Neg	Neg
SHOC2	SLE	M	13	Rash	Arthritis	Anaemia, thrombocytopenia, lymphopenia	Yes	Serositis	Serositis	No	LN type III	No	Low/ Low	1:2560	1:640	Ro+	IgG aCL, IgG aB2GP, LA
IFIH1 c.2807+1G>A	SLE	F	13	Oral ulcers	Arthralgia	Thrombocytopenia	No	No	No	No	No	No	Low/ Low	1:10240	1:1280	Neg	IgM aCL, IgM aB2GP, LA
TREX c.797A>G; TNFAIP3 c.1405C>G	Lupus-like	F	12	Rash, oral ulcers, lupus pernio	Arthralgia	No	No	No	No	Headache	No	No	Normal/ Normal	1:320	Neg	Neg	Neg
DNASE1 c.105G>C	Lupus-like	F	13	Malar rash	Arthritis	Thrombocytopenia, neutropenia, lymphopenia, hemolytic anemia	No	No	No	No	No	Autoimmune hepatitis	Low/ Normal	1:640	Neg	Neg	Neg
RNASEH2B c.868G>A; C1S c.619C>T	Lupus-like	M	9	No	Arthralgia	No	No	No	No	Headache	No	No	Low/ Normal	Neg	Neg	Neg	Neg
RNASEH2B c.868G>A; TLR7 c.3094G>A; STAT5A c.1248C>G	Lupus-like	M	8	No	Arthralgia	No	Yes	No	No	Headache	No	No	Low/ Normal	1:160	Neg	Neg	Neg
TREX1c.341G>A	Lupus-like	F	16	No	No	No	No	ILD	No	WMI	No	No	Normal/ Normal	1:320	Neg	Ro+	Neg
TNFRSF13B c.41G>A	Lupus-like	F	2	Rash	No	No	Yes	No	No	No	MP GMN	MAS, GG	Low Low	1:320	1:40	Ro+ La+	Neg

Conclusions Around 25% pediatric patients with cSLE or lupus-like phenotype in our cohort showed at least one variant in gene related to monogenic-lupus and some of them had a phenotype similar to those already described. The evidence of these variants may suggest the genetics potential contribution to the cSLE pathogenesis. Further studies in larger cohorts are necessary to confirm these data.

Thursday 06 October 2022 from 15:40 to 17:10

S11 immune system in SLE

S11.1 STRATIFICATION OF SYSTEMIC LUPUS ERYTHEMATOSUS (SLE) PATIENTS BASED ON THE MOLECULAR PATTERNS OF MOUSE MODELS

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Purpose Systemic lupus erythematosus (SLE) is an autoimmune, chronic and multisystemic autoimmune disorder, which typically affects women and presents high severity and mortality. It is characterized by the loss of self-tolerance, and both innate and adaptive immune systems contribute to its progression. SLE is considered a multifactorial disease as genetic, hormonal and environmental factors have been shown to contribute to its pathogenesis.

Mouse models have helped to understand the molecular mechanisms behind SLE and are commonly used to test new pharmaceutical compounds. However, the phenotype and molecular heterogeneity of SLE in humans limits its mimicking in animal models. Thus, we hypothesized that different mouse models might mimic better than others specific subgroups of SLE patients at the molecular level. The aim of this study is to characterize and compare different spontaneous mouse models at the molecular level and compare them with subgroups of human SLE patients.

Methods Four mouse models (MRL/lpr, NZB/W, BXSB.Yaa, and TLR7.Tg) were analyzed along four time points, including their respective genetic controls. The transcriptome (RNA-Seq) and cell proportions (flow cytometry) of the spleen, as well as numerous cytokines and autoantibodies in the serum were profiled. In addition, the molecular landscape of the mouse models was compared to SLE patients from the PRECISE-SADS project cohort.

Results Specific and shared molecular pathways were identified across the four mouse models. For example, upregulation of TNF signaling was shared by all models. On the other hand, BXSB.Yaa and TLR7.Tg shared the upregulation of leukocyte migration related genes, while the interferon-gamma response was only observed in the BXSB.Yaa and MRL/lpr mouse models. In addition, shared molecular pathways were dysregulated at different time points during the development of the phenotype. And as hypothesized, specific subgroups of SLE patients showed much closer molecular similarities to specific mouse models than others, thus allowing to stratify SLE patients based on the mouse models' dysregulated pathways.

Conclusion The results from this study constitute a molecular benchmark for future SLE mouse model studies. Relevant information is given about the choice of the model (out of the four included in the study), regarding the molecular pathway to be studied, and also about the time point when samples should be collected. In addition, we showed that different animal models at different stages present higher functional similarities with some subgroups of SLE patients than with others, which might improve the future translation of animal model results to the human disease.