PO.4.94 HIGH B-CELL POLYGENIC RISK IS ASSOCIATED WITH DSDNA ANTIBODIES AND NEPHRITIS IN SYSTEMIC LUPUS ERYTHEMATOSUS

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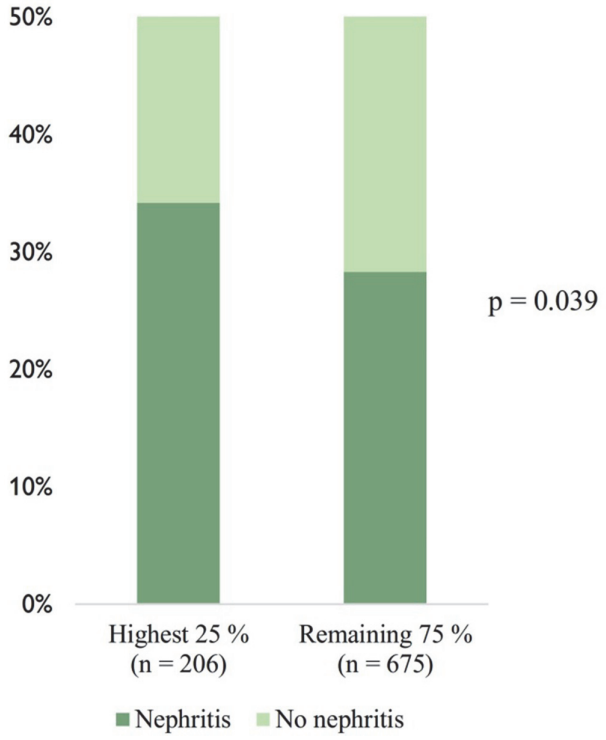
Purpose Lupus nephritis (LN) is a major clinical challenge and cause of significant morbidity and mortality in systemic lupus erythematosus (SLE). Today >180 SLE risk loci at Genome-wide significance (GWS, p < 5×10–8), including risk genes involved in B-cell function, have been identified. Associations between an individual's genetical burden and clinical manifestations in SLE can be studied using a polygenic risk score (PRS). In this study, we investigated associations between two SLE B-cell PRSs, SLE ACR-82 classification criteria, dsDNA antibodies and LN.

Methods Female SLE patients (n=1256) and healthy controls (n=519) from Scandinavia were genotyped using Illumina's Global Screening Array. Two PRSs were calculated1 for each individual, one including 21 GWS risk loci for SLE in genes assigned to B-cell related pathways (SLE B-cell PRS) according to the Kyoto encyclopedia of genes and genomes, Gene Ontology and Reactome databases, and one including a subset of 12 of these loci, limited to B-cell activation pathways (SLE B-cell activation PRS). High and low PRSs were defined as PRSs in the highest quartile and in quartile 1–3, respectively, and groups were compared by logistic regression (SPSS, version 28.0.1.0). A p-value < 0.05 was considered significant.

Results In total, 30% of patients had nephritis according to the ACR-82 criteria with an average age at nephritis onset of 33 years and dsDNA antibodies were more prevalent among patients with nephritis (78%) compared with patients without nephritis (56%) (OR 2.8 (2.0–3.9), p=2.1×10–10). The mean SLE B-cell PRS was higher in cases 2.9 (2.9–3.0) than controls 2.7 (2.6–2.7), (p = 4.1×10–11) and 11% of patients had an SLE B-cell PRS above the 95th percentile of controls. SLE was more prevalent in individuals with a high compared with a low SLE B-cell PRS (OR 1.8 (1.4–2.4), p=4.0×10–6).

The immunological criterion (ACR-82) was more prevalent among patients with a high compared with low SLE B-cell PRS (OR 1.4 (1.1–1.9), p = 0.013) and a similar association was found for dsDNA antibodies (OR 1.5 (1.1–2.0), p = 0.017). Numerically, a higher prevalence of nephritis was observed in patients with high compared with low SLE B-cell PRS, but it did not reach statistical significance (OR 1.2 (0.9–1.6), p = 0.19). However, the prevalence of nephritis was higher in patients with a high compared with a low SLE B-cell activation PRS (OR 1.3 (1.0–1.8), p = 0.039), Figure 1.

Conclusions High SLE polygenic risk related to B cell function is associated with development of dsDNA antibodies and nephritis in SLE. Assessing B-cell PRSs can be important in order to determine the immunologic pathways influencing the disease and to predict clinical phenotype.



Abstract PO.4.94 Figure 1 Prevalence of nephritis in patients with a B-cell activation PRS above the third quartile compared with patients in lower quartiles

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PO.4.95 CLUSTER-BASED GENOME-WIDE ASSOCIATION META-ANALYSIS IN EUROPEAN AND CHINESE DATASETS FOR SYSTEMIC LUPUS ERYTHEMATOSUS

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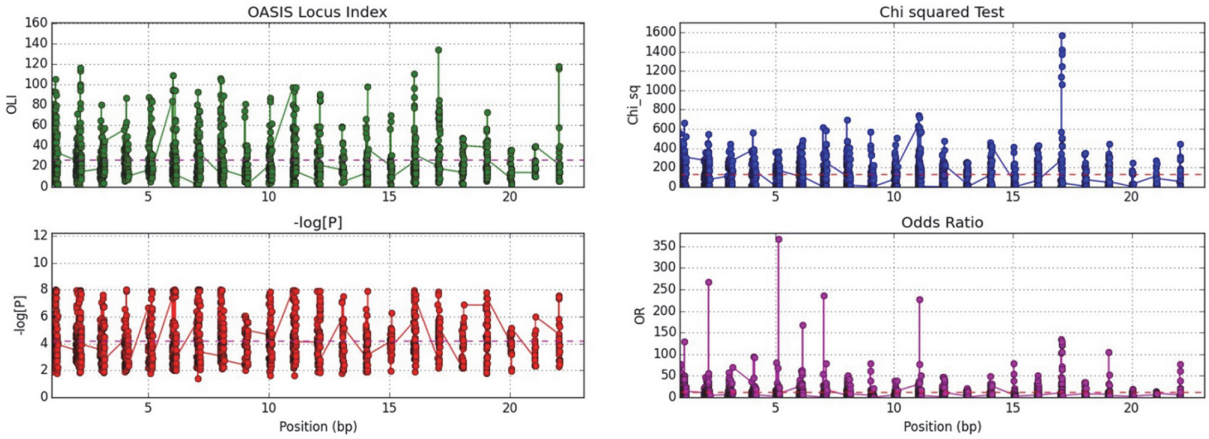
Purpose Systemic lupus erythematosus (SLE) is a complex disorder with significant genetic underpinnings that are only partially explained by multiple genome-wide association studies (GWAS). It is possible that several loci of modest significance remain to be discovered.

Methods GWAS meta-analyses of different populations teases out common loci. Moreover, association clustering methods such as gene- and locus-based tests are more powerful than single variant analysis for identifying modest genetic effects. Here, OASIS, a locus-based test, is applied to European (EU) and Chinese (Chi) GWAS to identify common significant non-HLA, autosomal genes/loci for SLE. OASIS was applied to six SLE dbGAP GWAS datasets, 4 EU and 2 Chi. Overall meta-analysis of 31,718 EU and 14,159 Chi subjects was



Abstract PO.4.95 Figure 1

performed. OASIS statistics used to identify significant loci included the novel OASIS locus index (OLI) defined as the product of maximum -logP at a locus with the ratio of actual to predicted number of significant SNPs. Chi-squared tests and odds ratios were also used to test the significance of loci.

Results Top non-HLA significant loci, common in both ethnicities were 2q32.2 (STAT4, rs11889341, P=10–65), 7q32.1 (IRF5, rs35000415, P=10–45) and 16p11.2 (ITGAM, rs1143679, P=10–47). Additionally, four loci strongly replicated in both ethnicities, identifying the known SLE genes: TNFSF4 (P=10–26), BANK1 (P=10–9), TNIP1 (P=10–17) and UBE2L3 (P=10–14). Other notable loci included 17p11.2 (TNFRSF13B (BLyS receptor), rs55701306, P=10–8, OR=14, OLI=66), 16p13.13 (CLEC16A, rs7186145, P=10–8, OR=9.7, OLI=54), 10q11.23 (WDFY4, rs1904605, P=10–7, OR=26, OLI=83) and 1q25.3 (NCF2, rs7552232, P=10–7, OR=42, OLI=89). Overall, OASIS identified 1488 modestly significant loci (P<10–8), of which 183 replicated in both ethnicities. This study will detail the results of these associated loci.

Conclusion Several genes and loci for SLE were identified using a cluster-based approach, OASIS, on six publicly available GWAS datasets from EU and Chi populations. This large meta-analyses will help comprehensive evaluation of SLE susceptibility genes.

PO.4.96 THE EPIGENOME OF SYSTEMIC LUPUS ERYTHEMATOSUS: MOLECULAR SUBTYPES, AUTOANTIBODY PROFILES, AND GENETIC INFLUENCES

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Purpose Systemic Lupus Erythematosus is a prototypic systemic autoimmune disease characterized by a complex aetiology and heterogeneous symptomatology. Epigenetic alterations are mediators of environmental and genetic factors and impact transcriptional programs. We aim to increase the knowledge of the contribution of epigenetics to SLE heterogeneity by studying its link with molecular subtypes, serological profiles, genetics and transcription, and use these data for drug discovery.

Methods Whole blood DNA methylation obtained with the Illumina HumanMethylation EPIC BeadChip was coupled with genetic and RNA sequencing data based on 213 SLE patients and 221 healthy controls from PRECISESADS. We performed epigenome wide association studies in a stratified fashion. We followed up results by conducting methylation quantitative loci analyses, cytokine-epigenetic associations, methylation-transcription factor activity correlations and the identification of new potential drug targets.

Results Differential methylation was observed at 974 CpG sites across the genome, many of them associated with SLE with dependence on the molecular subtypes and to a less extent to autoantibody profile. We discovered novel genetic loci associated with SLE that might exert their risk through DNA methylation changes, and a group of genetic variants that regulate DNA methylation in certain immunological or molecular contexts. Epigenetic associations with cytokine production and transcription factor activity also exhibit a high degree of specificity.

Conclusions This study expands the list of CpGs associated with SLE, with its heterogeneity revealing the pathways involved as well as the role of genetics regulating epigenetic signals, the influence of transcription factors shaping epigenomic landscapes and a group of cytokines that might be released as a consequence of epigenetic changes. This works discovers putative novel targets for drug discovery and biomarkers.