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

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10.1136/lupus-2022-elm2022.119

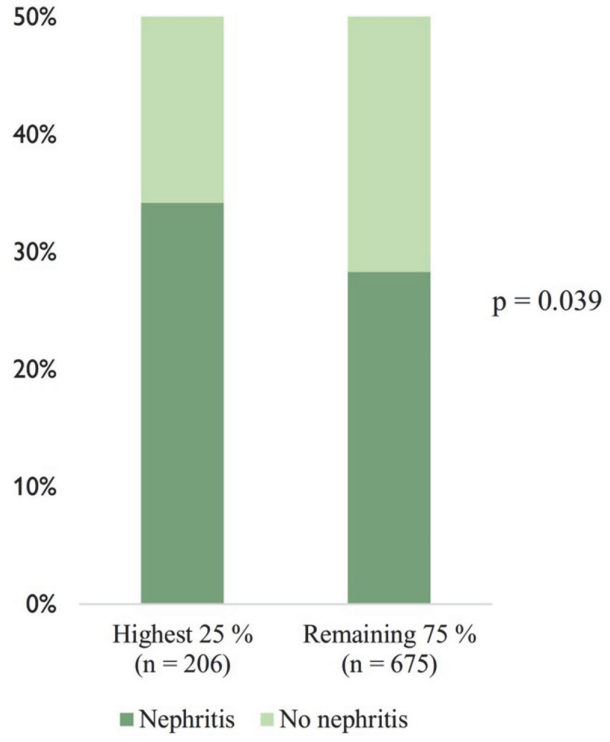
Purpose Lupus nephritis (LN) is a major clinical challenge and cause of significant morbidity and mortality in systemic lupus erythematosus (SLE). Today >180 SLE risk loci at Genome-wide significance (GWS, p < 5×10–8), including risk genes involved in B-cell function, have been identified. Associations 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

REFERENCES

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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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10.1136/lupus-2022-elm2022.120

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