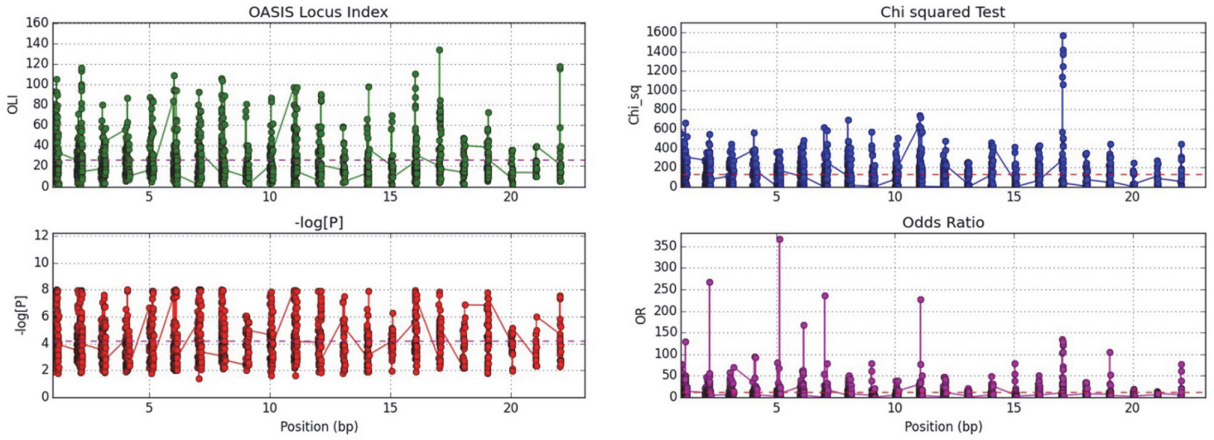

Abstract PO.4.95 Figure 1

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

[1]E Carnero-Montoro*, [1]O Castellini-Pérez, [1]G Barturen, [1]G Martínez-Bueno, [2]M Kerick, [3]A Iakovliev, [1]R López-Dominguez, [2]J Martin, [3]A Spiliopoulou, [4]E Derinaldis, [1]ME Alarcón-Riquelme. *[1]GENYO, Centre for Genomics and Oncological Research: Pfizer, University of Granada/Andalusian Regional Government ~ Granada ~ Spain; [2]IBPLN-CSIC, Instituto de Parasitología y Biomedicina López-Neyra ~ Granada ~ Spain; [3]Usher Institute of Population Health Science and Informatics. University of Edinburgh Medical School ~ Edinburgh ~ UK; [4]Sanofi ~ Boston ~ USA*

10.1136/lupus-2022-elm2022.121

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.