Background Genetic susceptibility of SLE in general is attributed to the overall risk of multiple common variants that each confers a small effect. However, in few cases, highly penetrant single gene variants have been reported as monogenic forms of SLE. To explore novel risk variants, we carried out whole-exome sequencing to identify underlying monogenic causes from two multiplex families that each family has two boys with childhood onset lupus nephritis.

Methods We sequenced the whole exome of lupus patients and their parents using the Illumina's instrument Hiseq2000. We conducted variant calling and annotation using the Genome Analysis Toolkit GATK and ANNOVAR, respectively. Our findings of exome-seq was confirmed using the Sanger sequencing.

Results Using bioinformatics, we focused only on potential loss-of-function variants. In addition, by using the recessive inheritance model and allele frequency <1% in population as filter, we identified potentially pathogenic variants from the SAT1 gene on chromosome X but not in previously known SLE-associated genes. In each family, we identified an exonic variant in an X-linked gene SAT1. These two variants presumably lead to the loss-of-function of SAT1. Both variants are inherited in the X-linked recessive pattern and they are extremely rare in the population (absent in >2 00 000 individuals). In one family, the SAT1 frameshift mutation was transmitted from the mother to the two sons affected with SLE but not to the unaffected son.

Conclusions We identified SAT1 as a novel gene associated with monogenic lupus. SAT1 encodes the spermidine/spermine-N1-acetyltransferase (SSAT), a rate-limiting enzyme that regulates the catabolism of polyamine. We hypothesize that loss-of-function SAT1 variants may cause dysregulated polyamine homeostasis which confers risk of SLE.

Abstract GG-04 Figure 1

GG-04 PATHOGENIC ROLE OF SAT1 VARIANTS IN MONOGENIC LUPUS

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GG-05 PREDICTIVE ABILITY OF SLE GENETIC RISK FACTORS VARIES ACROSS ETHNICITIES

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Background Systemic lupus erythematosus (SLE) exhibits marked ethnic disparities. The SLE Immunochip Consortium’s transancestral association study of SLE (27 574 individuals of European (EA), African (AA) and Hispanic Amerindian (HA) ancestry) raised the number of common risk variants to >100 (Langefeld 2017). There, we proposed the cumulative hit hypothesis, where the cumulative effect of individual loci is greater than if each locus acted independently. Here, we explore the joint contribution of SLE-susceptibility loci, how it varies by ethnicity, and whether there are distinct genetic risk profiles.

Methods The SLE Immunochip study design, identification of risk loci, and genetic load (risk allele count (RAC) in EA samples) were previously described (Langefeld 2017). Genetic load was tested for association with SLE in an independent set of 2000/2000 EA case/controls, and in the AA and HA cohorts. Individuals in lowest 10% of the RAC distribution were the reference sample. A logistic regression model, adjusting for admixture, computed the odds ratio (OR) comparing the reference group to samples within a moving window of 20 unweighted RAC (moving window of 4 for the weighted (SNP’s log(OR)) analysis). Lasso regression identified EA risk SNPs that maximally predict SLE status in EA, then applied prediction to AA and HA. Factor analysis identified individual genetic risk profiles.

Results The OR comparing lowest versus highest 10% of RAC was ~30, ~6, and ~3 for EA, HA and AA, respectively (figure 1), showing EA risk loci were not highly predictive of SLE risk in HA and AA. In EA, the moving window genetic load OR showed an increase beyond that predicted by independence but did not in HA and AA due to lower predictive ability. Lasso regression identified 51 risk alleles that maximally predicted SLE in EA, and a factor analysis identified seven
Background Systemic Lupus Erythematosus (SLE) is chronic autoimmune disease with heterogeneous disease manifestations and outcomes. We aimed to define how molecular differences underlie this clinical heterogeneity through an integrative approach leveraging methylation, genetic and phenotypic data from a well characterized multiethnic cohort of SLE patients.

Methods 274 participants were studied. We defined our phenotypic outcomes by clustering analyses. We performed principal component analysis on the ACR clinical criteria and used the top 2 eigenvectors as input for K-means clustering. We identified stable clusters based on a stability score >0.8 determined by a bootstrap resampling method. Our predictors were DNA methylation and genetic variation. DNA extracted from blood was analyzed on the illumina EPIC Beadchip. Single nucleotide polymorphism (SNP) genotype data was generated on the Affymetrix LAT1 World Array. Multivariate linear regression adjusting for population stratification, cell composition, sex, smoking history, and age was used to identify differentially methylated CpGs across clinical ACR criteria. We then investigated whether the differentially methylated CpG were under genetic control in a methylation quantitative trait loci analyses (cis-meQTLs).

Results We identified three stable clusters based on ACR criteria. Cluster 1 was characterized by a higher proportion of participants of white ethnicity with malar rash, photosensitivity, serositis, arthritis, oral ulcers and fewer serologies. Cluster 2 was characterized by a higher proportion of lupus nephritis and anti-dsDNA antibodies. Cluster 3 was characterized by higher proportion of hematologic manifestations, lupus nephritis, anti-dsDNA and anti-Sm antibodies. We identified 196 CpGs in 107 genomic regions that were differentially methylated between the clusters (FDR<0.05). Of these, pathway analysis revealed significant enrichment of genes relating to Type 1 interferon signaling and IFN-gamma (adjusted p<1E-08). Overall, Interferon-alpha responsive genes were hypomethylated in cluster 3, hypermethylated in cluster 1, with cluster 2 presenting an intermediate signature.

We then investigated whether the differentially methylated CpG were under genetic control in a cis-meQTLs analyses. This identified 542 cis-meQTL pairs (FDR<0.01) with 97 CpGs under proximal genetic control, which were enriched for IFN-alpha and IFN-gamma responsive genes (hypergeometric p<0.01).

Conclusion Overall, we identified three clinical relevant clusters in a multiethnic SLE cohort. The three clusters could be differentiated by 196 CpGs of which 97 were under genetic control and enriched for IFN-gamma and IFN-alpha responsive genes. This work helps to elucidate the epigenetic and genetic mechanism behind the role of Type 1 interferon in SLE pathology.