

uncorrelated risk profiles (one driven by HLA alleles and six by non-HLA loci). The lasso identified 31 (3 HLA) and 8 (no HLA) EA risk alleles as predictive in the HA and AA, respectively. Using predicted probabilities from the lasso in EA, the area under the ROC curve was 0.75 for EA, 0.72 for HA, and 0.60 for AA.

Conclusions The EA SLE risk loci are highly predictive in EA (with a greater than additive effect), modestly predictive in HA, and weakly predictive in AA. We posit that the SLE genetics of AA are meaningfully different from EA and HA, merit increased study, and will require ethnicity-informed treatment strategies.

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GG-06 INTEGRATIVE ANALYSIS OF MULTI-OMICS DATA IN AN ETHNICALLY DIVERSE LUPUS COHORT IDENTIFIES DISTINCT MOLECULAR SUBTYPES OF SLE

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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 subserologies. 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 $p < 0.01$).

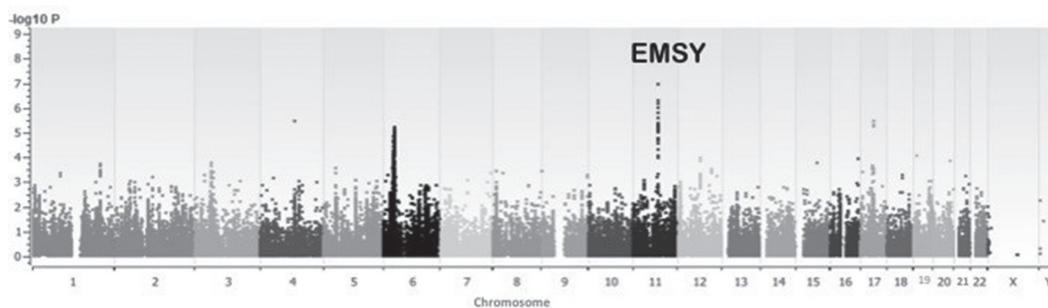
Conclusion Overall, we identified three clinical relevant clusters in a multiethnic SLE cohort. The three clusters could be differentiated by 196 CpGs of which 97 were under genetic control and enriched for IFN-gamma and IFN-alpha responsive genes. This work helps to elucidate the epigenetic and genetic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

GG-07 REGULATORY POLYMORPHISMS IN EMSY GENE ARE ASSOCIATED WITH AUTOANTIBODIES IN HEALTHY INDIVIDUALS

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Background Systemic lupus erythematosus (SLE) is characterized by the presence of multiple autoantibodies as well as clinical evidence of multi-system immune-mediated pathology. Individuals who develop SLE typically demonstrate serological



Abstract GG-07 Figure 1