

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

<sup>1,5</sup>Cristina Lanata\*, <sup>1,5</sup>Ishan Paranjpe, <sup>1</sup>Joanne Nititham, <sup>1</sup>Kimberly Taylor, <sup>2</sup>Brooke Rhead, <sup>1</sup>Milena Gianfrancesco, <sup>2</sup>Lisa Barcellos, <sup>3</sup>Louise Murphy, <sup>1</sup>Patricia Katz, <sup>1</sup>Maria Dall'Era, <sup>1</sup>Jinoos Yazdany, <sup>1</sup>Marina Sirota, <sup>1</sup>Lindsey Criswell. <sup>1</sup>University of California, San Francisco, USA; <sup>2</sup>University of California, Berkeley, USA; <sup>3</sup>Centers for Disease Control and Prevention, USA; <sup>4</sup>These authors contributed equally to this work

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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  $p < 0.01$ ).

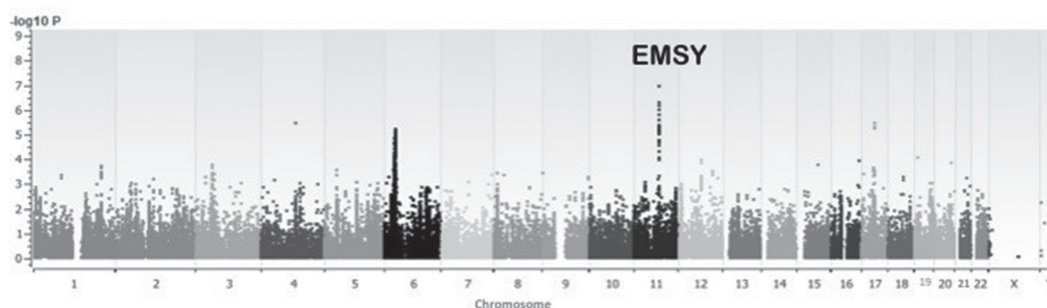
**Conclusion** Overall, we identified three clinical relevant clusters in a multiethnic SLE cohort. The three clusters could be differentiated by 196 CpGs of which 97 were under genetic control and enriched for IFN-gamma and IFN-alpha responsive genes. This work helps to elucidate the epigenetic and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

<sup>1</sup>Prithvi Raj, <sup>1</sup>Ran Song, <sup>1</sup>Benjamin E Wakeland, <sup>1</sup>Igor Dozmorov, <sup>1</sup>Kasthuribai Viswanathan, <sup>1</sup>Chaoying Liang, <sup>1</sup>Carlos Arana, <sup>1</sup>Bo Zhang, <sup>1</sup>JinChun Zhou, <sup>2</sup>Bernard R Lauwerys, <sup>3</sup>Nancy J Olsen, <sup>4</sup>Swapan Nath, <sup>5</sup>Peter K Gregersen, <sup>4</sup>Judith A James, <sup>6</sup>Betty P Tsao, <sup>4</sup>Patrick M Gaffney, <sup>7</sup>David R Karp\*, <sup>1</sup>Quan-Zhen Li, <sup>1</sup>Edward K Wakeland. <sup>1</sup>Department of Immunology, University of Texas Southwestern Medical Center, Dallas, TX, USA; <sup>2</sup>Pôle de pathologies, Institut de Recherche Expérimentale et Clinique, Brussels, Belgium; <sup>3</sup>Division of Rheumatology, Department of Medicine, Penn State Hershey Medical School, PA, USA; <sup>4</sup>Arthritis and Clinical Immunology Program, Oklahoma Medical Research Foundation, OK; <sup>5</sup>Feinstein Institute for Medical Research, Manhasset, NY, USA; <sup>6</sup>Department of Medicine, Medical University of South Carolina, Charleston, SC, USA; <sup>7</sup>Rheumatic Diseases Division, University of Texas Southwestern Medical Center, Dallas, TX, USA

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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

autoimmunity for several years prior to the onset of clinical disease. Measuring anti-nuclear antibodies (ANA) is a common test for humoral autoimmunity. It is sensitive (95+%) for SLE, but not specific as up to 25% of healthy controls (HC) will have a measurable ANA. While very few of the ANA +HC will develop SLE, they represent a group at higher risk of the disease. Understanding the risks for ANA positivity provides essential knowledge about the development of SLE.

**Methods** Serum and DNA were collected from 2903 healthy individuals with no personal history of autoimmunity. Antinuclear antibodies were detected using Inova QuantaLite ELISA. Sera from subset (n=724) individuals (ANA– HC, ANA+ HC, and SLE) were assayed by protein microarray quantifying IgM and IgG responses to 89 previously known human autoantigens. A nested cohort consisting of all the ANA +Caucasian individuals and age/gender matched ANA– controls were genotyped using the ImmunoChipv.1 SNP array.

**Results** In HC, 16% had moderate and 10% had high levels of IgG ANA. Autoantigen microarray data showed that ANA+ HC had a high prevalence of antibodies to non-nuclear and cytoplasmic antigens while subjects with SLE predictably produced antibodies to a variety of nuclear antigens as well. A quantitative genetic association test with ANA identified the locus *c11orf30* or *EMSY*, associated with high ANA phenotype in the healthy population (see figure 1). This locus codes for a negative transcriptional regulator. A haplotype comprised of many potentially regulatory polymorphisms at *EMSY* contributed to strong risk for ANA in healthy individuals [(p=3.83E-04, OR=2.6)]. eQTL data suggests that the ANA-associated *EMSY* haplotype leads to reduced expression of *EMSY* protein in human macrophages and EBV cell lines. Autoantibody profiles of serum samples from healthy individuals with the *EMSY* risk genotype exhibited high titers of anti-IgG and IgA antibodies targeted to multiple autoantigens as well as food and environmental allergens.

**Conclusions** *EMSY*, a locus previously linked with atopy, psoriasis and inflammatory bowel disease was associated with ANA in healthy individuals. The *EMSY* protein is a BRCA2-associated transcriptional repressor. Individuals with risk haplotypes in *EMSY* make a wide variety of disease-associated antibodies, suggesting an early common pathway for autoimmune and allergic conditions.

#### GG-08 IMMUNE REPERTOIRE AND GENETIC RISK ALLELES IN HEALTHY PEDIATRIC POPULATIONS WITH AUTOIMMUNE INDICATORS

<sup>1</sup>Prithvi Raj\*, <sup>1</sup>Patricia Pichilingue-Reto, <sup>1</sup>Igor Dozmorov, <sup>1</sup>Ran Song, <sup>1</sup>Chaoying Liang, <sup>1</sup>Carlos Arana, <sup>2</sup>Brandi Cantarel, <sup>2</sup>Daehwan Kim, <sup>1</sup>Bo Zhang, <sup>1</sup>JinChun Zhou, <sup>1</sup>Erika Molina, <sup>3</sup>Peter K Gregersen, <sup>4</sup>Judith A James, <sup>5</sup>David R Karp, <sup>6</sup>M Teresa de la Morena, <sup>1</sup>Quan-Zhen Li, <sup>6</sup>Nicolai SC van Oers, <sup>1</sup>Edward K Wakeland. <sup>1</sup>Department of Immunology, University of Texas Southwestern Medical Center, Dallas, TX USA; <sup>2</sup>Department of Bioinformatics, University of Texas Southwestern Medical Center, Dallas, TX USA; <sup>3</sup>Feinstein Institute for Medical Research, Manhasset, New York USA; <sup>4</sup>Oklahoma Medical Research Foundation, Oklahoma City, OK USA; <sup>5</sup>Rheumatic Diseases Division, University of Texas Southwestern Medical Center, Dallas, TX USA; <sup>6</sup>Department of Pediatrics, University of Texas Southwestern Medical Center, Dallas, TX USA

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**Background** The antibody specificities of an infant progressively form in response to infections, environmental exposures, and vaccinations. While many adults develop antibodies to self-antigens, it remains unknown if these are present in infants and toddlers.

**Methods** Serum, peripheral blood, and clinical data have been collected from 102 healthy children (1–2 year of age). ANA titers were measured by QuantiaLite ELISA (Inova) and reactivity to 125 diverse autoantigens tested by autoantibody array. Targeted sequencing was performed in 60 children to capture HLA alleles and potentially pathogenic genetic variations in 100 plus loci that are implicated in various autoimmune, rheumatic and immune system related diseases. Sequencing libraries were made using KAPA Biosystems kits. Custom target oligos were synthesized from Nimblegen. Deep sequencing was performed using Illumina HiSeq 4000 platform. Sequencing reads were aligned to reference genome and variants were called using GATK Pipeline. Secondary data analysis is done using Metlab, GraphPad Prism, Haploview and Golden Helix programs.

**Results** Approximately 28% of very young children have moderate to high-titer autoantibodies, similar to adults, however, no female gender bias was observed. Significant differences between the child and adult immune repertoires were seen. Some samples demonstrated strong signatures of non-nuclear antigens reactivities. Interestingly, the ANA positive group of children exhibited significantly high titers of anti-alpha fodrin IgG (p=0.01), an autoantibody reported in juvenile Sjogren's syndrome. Analysis of sequencing data identified regulatory polymorphisms in HLA class II and III regions that were associated with ANA positivity. About 8% of the ANA positive children also carried autoimmune disease associated HLA-DR-DQ alleles. HLA alleles and regulatory haplotypes were analyzed in relation to various clinical features in children. Serum C4 level measured in subset of ANA positive children identified few with reduced expression.

**Conclusions** While the immune repertoire of very young children is typically thought of as naïve and self-tolerant, a significant fraction of very young children makes autoantibodies as detected by commercial ANA ELISA and autoantigen arrays. This supports the conclusion that ANA and other autoantibodies are consequences of general body development and immune upregulation and not markers of pathology. One of the major genetic determinants of 'pre-clinical' autoimmunity as measured by ANA is the human major histocompatibility locus, *HLA*. Within *HLA*, several 'endophenotypes' emerge, including expression of a complement protein involved in immune complex removal, as well as multiple proteins associated with antigen presentation, including MHC class II. These findings support the idea that there is quantifiable genetic risk for the development of autoimmunity that can be measured in very young individuals.

#### GG-09 A ROLE FOR EBNA2 IN MECHANISMS THAT ARE RESPONSIBLE FOR LUPUS AND OTHER AUTOIMMUNE DISEASES

<sup>1,2,3,4,5</sup>JB Harley\*, <sup>1</sup>X Chen, <sup>1</sup>M Pujato, <sup>1</sup>D Miller, <sup>1</sup>A Maddox, <sup>1</sup>C Forney, <sup>1</sup>AF Magnusen, <sup>1</sup>A Lynch, <sup>6</sup>K Chetal, <sup>7</sup>M Yukawa, <sup>4,7,8</sup>A Barski, <sup>4,6</sup>N Salomonis, <sup>1,2,4,5</sup>KM Kaufman, <sup>1,4</sup>LC Kottyan, <sup>1,3,4,6</sup>MT Weirauch. <sup>1</sup>Center for Autoimmune Genomics and Etiology (CAGE); <sup>2</sup>Division of Immunobiology; <sup>3</sup>Division of Developmental Biology, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio; <sup>4</sup>Department of Pediatrics, University of Cincinnati, Cincinnati, Ohio; <sup>5</sup>US Department of Veterans Affairs Medical Center, Cincinnati, Ohio; <sup>6</sup>Division of Biomedical Informatics; <sup>7</sup>Division of Allergy and Immunology; <sup>8</sup>Division of Human Genetics, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA

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**Background** Explaining the genetics of many diseases is challenging because most associations localize to incompletely understood regulatory regions.