GG-04 PATHOGENIC ROLE OF SAT1 VARIANTS IN MONOGENIC LUPUS

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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-N^1-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.

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

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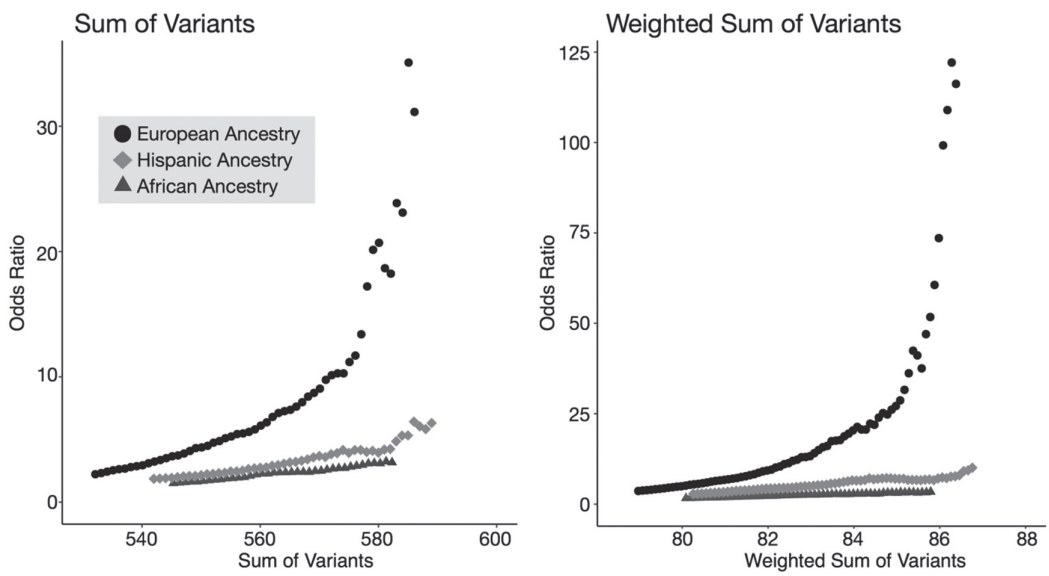
Background Systemic lupus erythematosus (SLE) exhibits marked ethnic disparities. The SLE Immunochip Consortium's transancestral association study of SLE (27 574 individuals of European (EA), African (AA) and Hispanic Amerindian (HA) ancestry) raised the number of common risk variants to >100 (Langefeld 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



Abstract GG-05 Figure 1