

analysis). Between wk24 and wk48, response rates across disease measures were either sustained (e.g. SRI-4, 62% at wk24 vs 63% at wk48; joint response 87% at wk24 vs 87% at wk48) or increased (CLASI response, 53% at wk24 vs 69% at wk48) in those randomized to UST. Following crossover at wk 24, an additional 10%–20% of PBO patients responded to UST (n=33) in the outcomes studied. Clinical response to UST was associated with decreases in IFN- protein and gene signature. In contrast, IFN-I levels were stable over time and were not associated with UST response. Safety events were consistent with the known UST safety profile.

Conclusions UST provided sustained clinical benefit in global and organ (mucocutaneous and joint disease)-specific SLE activity measures with a safety profile consistent with approved indications. Thus, UST may be an effective biologic therapy for SLE by blocking IL-12 and IL-23-driven pathogenic mechanisms which are independent of the IFN-I pathway.

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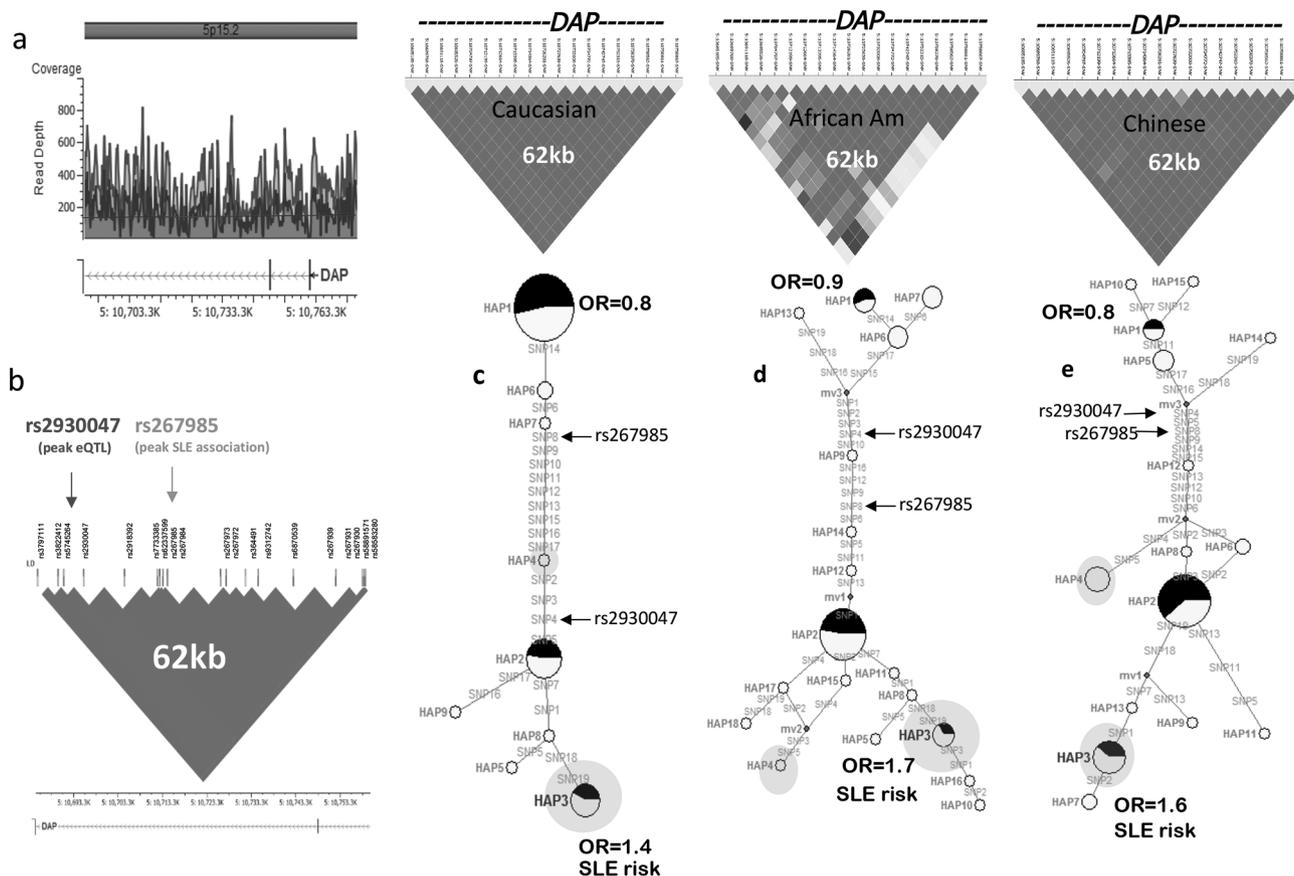
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202 TARGETED SEQUENCING IN 1200 SLE PATIENTS REVEAL DAP1 REGULATORY HAPLOTYPE THAT POTENTIATE AUTOIMMUNITY

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Abstract 202 Figure 1 SLE associated DAP1 haplotype in Caucasian, African American and Asian population. Panel a: shows the sequencing depth across DAP1 gene locus on chromosome 5. Panel b: shows the 62kb LD (Linkage Disequilibrium) block that contain top 19 SLE associated variants (rsIDs shown). The peak SLE associated SNP rs267985 and strongest DAP1 eQTL rs2930047 are shown. Panel c: Median-joining (MJ) network analysis on most common DAP1 haplotypes in Caucasian SLEs and healthy controls. Spheres (termed nodes) represent the locations of each haplotype (from Table 2) within the network and the size of the node is proportional to the overall frequency of that haplotype in the dataset. Each node is overlaid with a pie chart that reflects the frequency of that haplotype in SLE group (yellow) versus healthy group (black). The lines connecting the nodes are labeled with the variants that distinguish the connected nodes and the length is proportional to the number of variants. Odds ratio (OR) are shown for two most significant alleles. Red highlighted nodes indicate SLE risk clades. . Panel d: Median-joining (MJ) network analysis on most common DAP1 haplotypes in African American SLEs and healthy controls. . Panel e: Median-joining (MJ) network analysis on most common DAP1 haplotypes in Asian SLEs and healthy controls.

Background Systemic lupus erythematosus (SLE) is characterized by the presence of autoantibodies and multi-system immune-mediated pathology. Genome-wide association studies have identified >60 SLE risk loci, suggesting a polygenic susceptibility. Although these loci account for significant genetic heritability, a large proportion is still missing. The missing heritability can be explained by the genetic component of intermediate phenotypes contributed by low frequency functional variants not captured on classical SNP arrays. Deep targeted sequencing of SLE associated genes allows comprehensive and personalized assessment of genetic risk by annotating all common and rare disease causing variants. This study was performed to investigate functional variants in the gene for Death associated protein 1 (DAP1) that was previously implicated in susceptibility to SLE.

Methods We performed deep targeted sequencing of the DAP1 locus in 1221 SLE and 814 healthy control samples capturing both common and rare SLE associated variants. Genetic association analysis was carried out to identify disease associated haplotypes. SLE associated variants were annotated for functional effects using publically available resources and an eQTL panel of healthy donors. Serum autoantibody signatures and gene expression profiles of SLE patients carrying SLE risk or protective genotypes were analyzed in combination with the level of DAP1 transcription and translation. Since DAP1 protein is a potent negative regulator of autophagy, the effect of its downregulation in the risk group, was assessed in a functional autophagy assay.

Results Sequencing of the DAP1 gene revealed a novel, functional haplotype that poses risk [OR=1.5, $p=4.5E-05$] for SLE. The association was replicated in two independent cohorts of patients from different ethnic groups. RNA sequencing analysis revealed multiple cis-eQTLs embedded in the risk haplotype that downregulate DAP1 expression in immune cells. Decreased DAP1 transcription in the risk allele was consistent with reduced protein level. Healthy donors with the DAP1 risk genotype had a significantly elevated ratio of LC3-II/LC3-I in PBMCs and monocytes under starvation, suggesting enhanced autophagy mediated by the risk haplotype. SLEs with the risk genotype exhibited significantly high autoantibody titers and altered expression of autophagy and apoptosis pathway molecules.

Conclusions This study reports a regulatory haplotype in the DAP1 locus associated with a reduced DAP1 protein level and enhanced autophagy in immune cells that can promote survival of autoreactive lymphocytes and potentiate autoimmunity.

Funding Source(s): Alliance for lupus research, NIH, UTSW

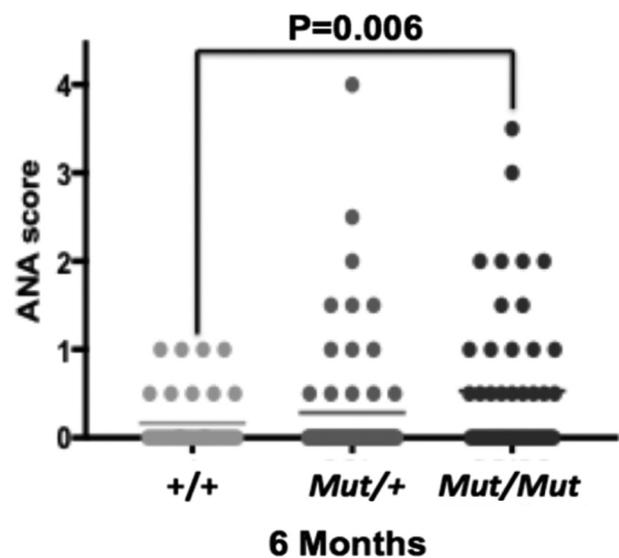
203 A MISMATCH REPAIR GENETIC VARIANT IS LINKED TO THE DEVELOPMENT OF LUPUS

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Background Recent analysis of exome chip data indicates that genetic variants (GVs) in DNA repair genes are enriched in individuals diagnosed with systemic lupus erythematosus (SLE). **Methods** Specifically, we analyzed 1364 single nucleotide polymorphisms (SNPs) within 41 genes that function in DNA repair. In a comparison of 1,201 SLE cases to 597 controls, corrected for ancestry, we identified 9 GV's with odds ratios (ORs) ranging from 1.1–4.6 in genes that function in mismatch repair as being significantly enriched in SLE cases versus controls. We followed up this analysis with replication studies, by analyzing a second cohort of individuals with 1298 SLE cases and 633 controls, and we were able to replicate our initial findings with full ORs ranging from 2 to 8.393.

Results One of the variants that emerged from our exome chip (eChip) studies is the MSH6 GV. This variant is a single amino acid change in the DNA binding domain of the MSH6 protein that is predicted to be damaging using the POLYPHEN algorithm. The MSH6 GV is eight times more prevalent in human SLE versus control cases after correcting for ancestry (odds ratio [OR]=8.393; $p=0.0398$). Remarkably, among the 2499 cases in the combined cohort, patients harboring the MSH6 GV are diagnosed with lupus 11.2 years earlier than SLE patients not harboring this allele ($p=0.004$). To determine if the MSH6 GV is linked to the development of lupus, we employed CRISPR/cas9 gene-editing technology to construct a mouse harboring this variant. Initial characterization of the mice shows that they develop significantly



Abstract 203 Figure 1 High levels of ANA in MSH6 GV mice