Results Four SLE-risk genes were found to be associated with a decreased time until the first MI; PTPN22 (OR 1.61, p=0.0041), NCF2 (OR 2.47, p=2.1×10^{-5}), STAT4 (OR 1.66, p=5.2×10^{-5}) and IL12A (OR 1.45, p=0.047) and were included in a PRS. The PRS was associated with a higher cumulative prevalence of MI in both the discovery cohort (p=1.1×10^{-5}, fig 1A) and replication cohort (p=7.7×10^{-5}, fig 1B). Exploring the PRS further in the replication cohort, patients in the high, compared to the low, PRS-quartile were more often male (p=1.3×10^{-5}), and displayed higher prevalence of the ACR-1982 nephritis and immunological criteria (p=4.1×10^{-4} and p=0.036) (fig 1C).

Conclusion A high polygenic risk score for MI in SLE is associated with an increased prevalence of myocardial infarction. If confirmed in prospective studies, our results suggest that genetic profiling may be useful for predicting MI in patients with SLE.

P92 GENOMIC CONVERGENCE OF LOCUS-BASED GWAS META-ANALYSIS IDENTIFIES DDX11 AS A NOVEL SYSTEMIC LUPUS ERYTHEMATOSUS GENE

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Background Systemic lupus erythematosus (SLE) is a complex autoimmune disorder with significant genetic underpinnings. Multiple genome-wide association studies (GWAS) have been conducted with identification of several SLE genes and loci. However, these only explain about 15% of SLE genetic risk indicating that additional loci of modest effect remain to be discovered. Association clustering methods such as OASIS are more apt than single-variant analysis for identifying modest genetic effects.

Methods Previously, OASIS analysis of two dbGAP GWAS datasets (6077 subjects; 0.75 million single-nucleotide polymorphisms (SNPs)) identified 30 SLE associated loci. In the Cordoba dataset, 10 genes were found to have altered expression in SLE patients in the high, compared to the low, PRS-quartile were more often male (p=1.3×10^{-5}), and displayed higher prevalence of the ACR-1982 nephritis and immunological criteria (p=4.1×10^{-4} and p=0.036) (fig 1C).

Conclusion A high polygenic risk score for MI in SLE is associated with an increased prevalence of myocardial infarction. If confirmed in prospective studies, our results suggest that genetic profiling may be useful for predicting MI in patients with SLE.

P93 ANALYSIS OF LOW-FREQUENCY AND RARE VARIANTS IN SWEDISH SLE PATIENTS WITH LUPUS NEPHRITIS

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Background Genome wide association studies (GWAS) have identified numerous SLE risk genes, however, few genes are reported as predisposing to the lupus nephritis (LN) phenotype.

Objective To explore whether gene-based aggregates of low frequency (MAF<0.05) and/or rare (MAF<0.01) single nucleotide polymorphisms (SNPs) were associated with different subsets of LN or end stage renal disease (ESRD).

Methods We analyzed genotype data from Swedish SLE patients (n=958). Data was generated by targeted sequencing of the coding and regulatory regions of 1900 genes involved in basic immune functions, inflammation and autoimmune diseases. The softwares GenPy² and optimized sequence Kernel association test (SKAT-O)³ were used to analyze the impact of low frequency and rare variants in LN patients with different sub-phenotypes (n=208) as compared to those (n=621) who had not developed LN at the time of the study. We also performed logistic regression models with different sub phenotypes of LN as the outcome, adjusted for sex and age.

Results Two candidate genes; gelsolin (GSN; 5.97×10^{-5}) and insulin like growth factor binding protein 7 were identified (IGFBP7; 5.95×10^{-5}) to have significantly higher GenePy scores in cases vs controls (bootstrap test, 1000 permutations). GSN, an actin-binding protein, is involved in non-AL renal amyloidosis and in the development of IgA nephropathy. GSN was associated with proteinuria [OR, 95% CI]; 14.1 [2.9–66.9]), p=0.001 and ESRD (5.9{2.4–15.0}, p=0.001) after adjusted for gender and age. IGFBP7, an emerging biomarker for acute kidney injury, was also significantly associated with Class3/4 and ESRD (p=4.9×10^{-5}). SKAT-O identified one gene was associated with Class V; CTF1 (suggestive p<2.97×10^{-5}, Bonferroni corrected p=0.05).

Conclusion An aggregate association testing approach incorporating functional annotation revealed two putative risk loci (GSN and IGFBP7) associated with LN and ESRD. Further investigation needs to test their functional roles in detail.

REFERENCES