Novel Gene Variants Associated with Cardiovascular Disease in Systemic Lupus Erythematosus and Rheumatoid Arthritis - Supplementary file

Supplementary tables

Supplementary table S1. Age at first cardiovascular event

	Discovery cohort (Sweden)
PE/DVT (yr.)	42±16
MI/angina (yr.)	58±15
Stroke/TIA (yr)	52±17
Stroke/MI (yr.)	54±17

Patients in the discovery cohort. Data are mean±SD. PE, pulmonary embolism; DVT, deep vein thrombosis; MI, myocardial infarction; TIA, Transient ischemic attack.

Supplementary table S2. Clinical characteristics of the patients with Rheumatoid Arthritis

Number of patients	837
Female	586 (70)
Age at diagnosis (yr.)	55.2±14.3
Disease duration* (yr.)	7.5±3.9
ACPA	582 (71.3)
Stroke/MI	73(8.7)
MI/angina/intervention	54 (6.5)
Stroke/TIA	46 (5.5)

Data are number (%) or mean ± SD; ACPA, Anti-citrullinated protein antibodies; MI, myocardial infarction; TIA, Transient ischemic attack; MI, myocardial infarction;* Time after onset of RA until CVD-event, death or end of study. Genetic data missing for 13 patients. Patients with stroke or MI before RA diagnosis were excluded.

Supplementary table S3. Definitions of cardiovascular events in SLE

Myocardial infarction (MI),	Increase plasma troponin T or creatine kinase, muscle and brain fraction, and one of the following: symptoms of ischemia, ECG changes, development of pathological Q wave or new regional wall motion abnormality.
Angina pectoris (angina)	Confirmed by exercise stress test.
Ischemic stroke (stroke)	Confirmed by computer tomography or magnetic resonance imaging.
Transient ischemic attack (TIA)	Transient focal symptoms from the brain or retina with a maximum duration of 24 hours
Pulmonary embolism (PE)	Confirmed by radionuclide lung scanning or angiogram.
Deep vein thrombosis (DVT)	Confirmed by venography or ultrasonography.

Supplementary table S4. Stroke and/or myocardial infarction, multiple logistic regression, discovery cohort.

	Univariate		Multivariable	
Risk factor	OR (95%CI)	p-value	OR (95%CI)	p-value
Gender (female)	0.83 (0.50 – 1.46)	0.48	0.61 (0.39 – 1.33)	0.22
Age years	1.06 (1.04 – 1.07)	5.28×10^{-16}	1.06 (1.04 – 1.08)	1.11×10^{-8}
Smoking ever	1.70 (1.17 – 2.50)	6.15×10^{-3}	1.24 (0.77 – 1.99)	0.38
Hypertension treatment	5.28 (3.50 – 8.11)	7.21×10^{-15}	2.72 (1.64 – 4.51)	1.12×10^{-4}
Diabetes	4.27 (2.17 – 8.29)	1.89×10^{-5}	1.86 (0.82 – 4.21)	0.14
Nephritis*	1.51 (1.03 – 2.21)	3.20×10^{-2}	2.35 (1.37 – 4.03)	1.96×10^{-3}
aPL**	1.72 (1.13 – 2.59)	1.00×10^{-2}	1.88 (1.15 – 3.06)	1.18×10^{-2}
IL19 risk locus***	2.09 (1.25 – 3.42)	3.79×10^{-3}	2.03 (1.07 – 3.84)	3.09×10^{-2}

Discovery cohort (n= 814); *ACR criteria number 7[1]; **aPL, antiphospholipid antibodies (at least one positive test for anti-cardiolipin (IgM or IgG) or anti-β_2 glycoprotein-I (IgG)); ***rs74148801 CC/CT/TT.

Supplementary table S5. The *IL19* and *SRP54-AS1* risk variants in SLE and healthy controls

SNP	Locus	M/m	MAF	OR(CI)	P
rs17581834	*IL19*	C/T	0.057/0.051	1.11(0.90-1.37)	0.33
rs799454	*SRP54-AS1*	A/G	0.406/0.411	0.98(0.88-1.08)	0.68

The *IL19* SNP rs17581834 associated with stroke/MI in SLE and RA and the *SRP54-AS1* SNP rs7994543 associated with stroke/TIA in SLE. 1045 patients with SLE and 2711 healthy controls. M/m, major/minor alleles; MAF, minor allele frequency for SLE/healthy controls; P, p-value unadjusted.

Supplementary table S6. Association between the SLE ACR-criteria and the *IL19* and *SRP54-AS1* risk alleles

	IL19, rs17581834		SRP54-AS1, rs799454	
ACR criteria	OR(95%CI)	p-value	OR(95% CI)	p-value
1) Malar rash	0.91(0.57-1.45)	0.70	0.99(0.81-1.21)	0.93
2) Discoid rash	1.12(0.65-1.92)	0.69	0.84(0.67-1.07)	0.16
3) Photosensitivity	1.09(0.66-1.80)	0.74	0.90(0.73-1.11)	0.32
4) Oral Ulcers	1.07(0.64-1.81)	0.79	0.95(0.76-1.18)	0.63
5) Arthritis	0.70(0.41-1.18)	0.18	1.06(0.83-1.35)	0.63
6) Serositis	0.69(0.43-1.12)	0.13	1.04(0.86-1.27)	0.69
7) Renal disorder	1.34(0.83-2.15)	0.23	0.96(0.78-1.18)	0.67
8) Neurologic disorder	0.67(0.27-1.70)	0.41	0.79(0.56-1.11)	0.17
9) Hematologic disorder	1.49(0.90-2.47)	0.12	1.05(0.85-1.28)	0.67
10) Immunologic disorder	0.73(0.45-1.17)	0.19	1.13(0.92-1.40)	0.26
11) Positive ANA	1.00(1.00-1.00)	1.0	0.71(0.34-1.52)	0.38

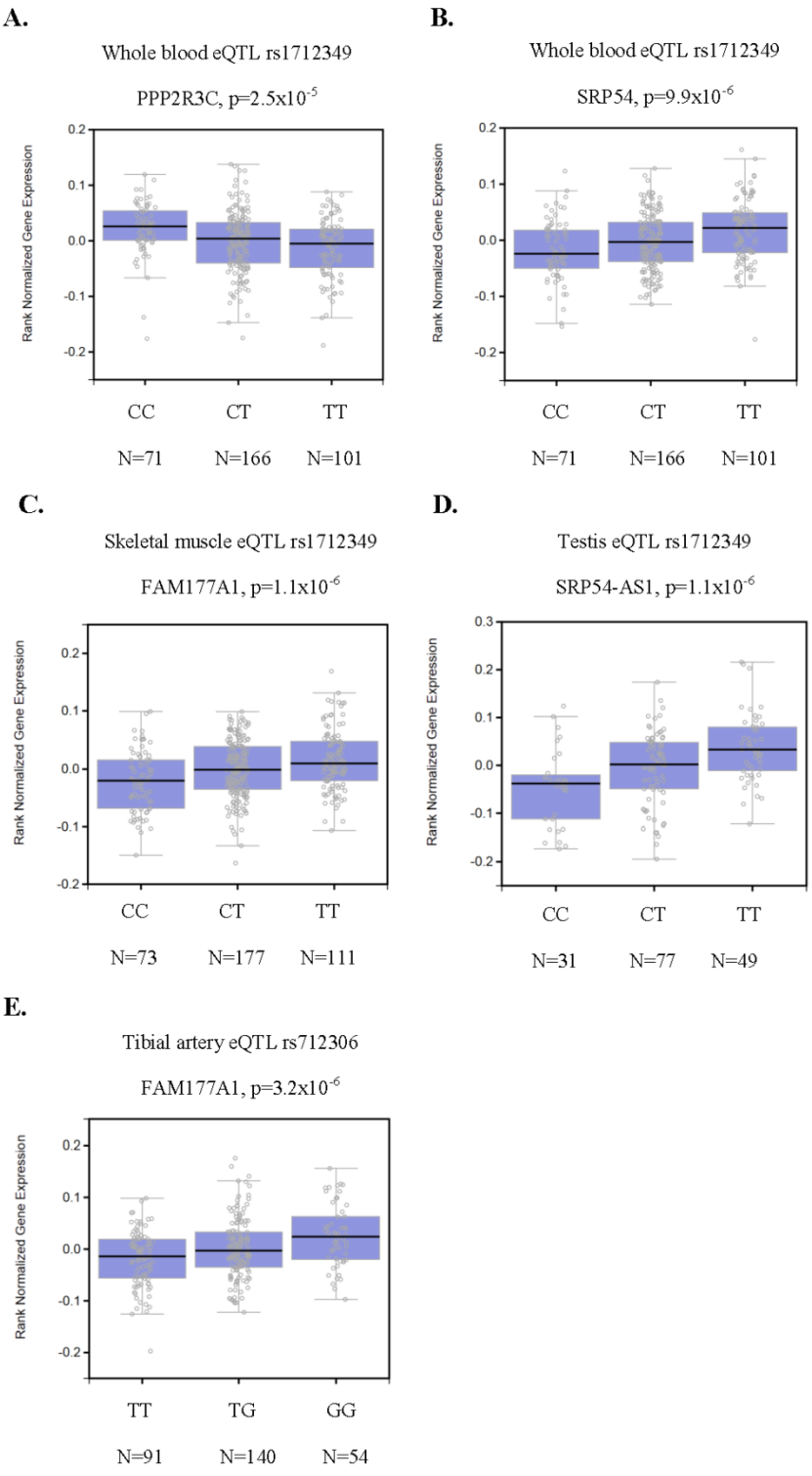
1045 patients in cohort 1; ACR criteria.[1]

Supplementary table S7. Stroke and/or TIA, multiple logistic regression, discovery cohort.

	Univariate		Multivariable	
Risk factor	OR (95%CI)	p-value	OR (95%CI)	p-value
Gender (female)	0.82 (0.46 – 1.56)	0.54	0.61 (0.27 – 1.37)	0.23
Age years	1.04 (1.03 – 1.06)	4.00×10^{-9}	1.05 (1.03 – 1.07)	2.91×10^{-6}
Smoking ever	1.26 (0.82 – 1.95)	0.28	1.11 (0.66 – 1.87)	0.69
Hypertension treatment	4.21 (2.67 – 6.81)	1.57×10^{-9}	2.25 (1.28 – 3.93)	4.60×10^{-3}
Diabetes	3.20 (1.48 – 6.53)	1.94×10^{-3}	1.89 (0.80 – 4.47)	0.15
Nephritis*	1.60 (1.03 – 2.46)	3.34×10^{-2}	2.93 (1.63 – 5.29)	3.51×10^{-4}
aPL**	1.69 (1.06 – 2.66)	2.58×10^{-2}	1.65 (0.97 – 2.80)	0.067
SRP54-AS1 risk locus***	1.94 (1.43 – 2.63)	1.94×10^{-5}	1.65 (1.15 – 2.37)	6.10×10^{-3}

Discovery cohort (n= 814). *ACR criteria number 7[1]; **aPL, antiphospholipid antibodies (at least one positive test for anticardiolipin (IgM or IgG) or anti-β_2 glycoprotein-I (IgG)); ***rs1712349 (CC/CT/TT).

Supplementary figure 1



Supplementary figure 1. GTEx expression QTLs for the *SRP54-AS1* risk locus. A. Whole blood expression of protein phosphatase 2 regulatory subunit B gamma (PPP2R3C). B. Whole blood expression of signal recognition particle 54 (SRP54). C. Skeletal muscle expression of family with sequence similarity 177 member A1 (FAM177A1). D. Testis expression of signal recognition particle 54 – antisense 1 (SRP54-AS1). Ref. = reference allele (C); Alt. = alternative allele (T). E. GTEx expression QTLs for FAM177A1 in tibial artery. The eQTLs rs712306 for FAM177A1 in LD (r^2=0.7) with rs1712349, the alternative (G) allele correlate with higher gene expression.

Supplementary– results

CVD in the general population – method and results

The *IL19* risk SNPs and the *SRP54-AS1* risk SNPs were examined for association with CVD in the general population using publicly available data. Summary data from meta-analysis of coronary artery disease (CAD) was downloaded from the CARDIoGRAMplusC4D Consortium web page http://www.cardiogramplusc4d.org/data-downloads/.[2] The CARDIoGRAM[3] data set, including results from a meta-analysis of 14 genome-wide association studies of CAD (n=86,995), showed no association between CAD and the *IL19* risk allele, rs11119598 (p=0.88) or the *SRP-54-AS1* risk allele, rs1712349 (p=0.74).

Next, the *IL19* risk alleles and *SRP54-AS1* risk alleles were analyzed for association with ischemic stroke using publicly available data on the International stroke genetics consortiums (ISGC) online platform, http://cerebrovascularportal.org/home/portalHome.[4] No associations between ischemic stroke and the *IL19* risk allele, rs11119598 or the *SRP54-AS1* risk allele, rs1712349 were observed in the SiGN[5] data set (n=49,324) (*IL19*, p=0.29 and *SRP54-AS1*, p=0.93) or in the METASTROKE[6] dataset (n=29,633) (*IL19*, p=0.62 and *SRP54-AS1*, p=0.87).

The Interleukin 7 receptor locus

The interleukin 7 receptor (*IL7R*) risk alleles was associated with stroke/TIA in both cohorts and in the meta-analysis OR (CI) 1.9(1.3-2.5), $p=2\times10^{-4}$ (table 3). However, when including the *IL7R* risk allele in a multivariable regression model together with traditional CVD risk factors the

association did not remain significant (data not shown). Further the *IL7R* risk allele was not in high LD with the gene variants previously shown to be associated with multiple sclerosis[7] and SLE.[8] Using EMSA we found no allele specific protein binding at the *IL7R* risk locus and it was not an eQTL (GTEx; data not shown).[9] Given these results we find this risk locus less likely to be of importance for development of CVD in SLE.

Supplementary methods

The RA cohort

Patients with early RA (1987 ACR criteria,[10] <12 months of symptoms) were consecutively included from the four most northern counties from Sweden since December 1995 into a national register. They were followed prospectively for disease progression, treatment and co-morbidity into a local register. Of the 1054 patients 899 had donated DNA and were analyzed for genetic polymorphisms using Immunochip Illumina (SNP&SEQ Technology Platform Uppsala, Sweden).[11] The follow-up started at inclusion and ended at the first myocardial infarction or angina, death or December 31 2011 by co-analyzing with the national registers of hospitalization and death in Sweden using classification of diseases (ICD-9 and 10) in 897 patients. Patients with a CV event before the diagnosis of RA were excluded from the analysis (n=60), leaving 837 patients. Genetic data was missing for 13 patients leaving 824 individuals for the logistic regression analysis of the 6 SNPs.

The diagnosis of stroke, transient ischemic attacks, myocardial infarction, angina pectoris with intervention (coronary artery bypass graft or percutaneous coronary intervention)**,** were defined according to ICD-9 (410, 411 A, B, C, 415B, 431, 432 (A, B,X), 433, 434, 437 B, 436, 444, 452, 453 (A-X); 451B; 557A,B;) and ICD-10 (I20 with Z951, 955 or FNGV9250.1-V9250.3, I21.0-21.9, I24.1, I 24.8-24.9, I26.0, I26.9, I61 (1, 2, 3, 8, 9) –I 67.2, I67.9, I74.0, I80.1- I80.3 with J81.9, G45.8, 45.9, K55.0, 55.1).

Genotyping and quality control

Genotyping was performed with the Immunochip (an Illumina iSelect custom array designed by the ImmunoChip Consortium).[12] Genotyping for the discovery cohort and the RA cohort was

performed at the SNP&SEQ Technology Platform at Uppsala University, Sweden and genotyping for the replication cohort was performed at the Feinstein Institute for Medical Research, HudsonAlpha Institute for Biotechnology, and the University of Texas Southwestern Medical Center, USA.

Quality control (QC) for the Discovery cohort

Sample call rate below 95% and SNPs with call rate below 98% were excluded. Samples with abnormal autosomal heterozygosity rate with more than 5SD from the mean of Wright's inbreeding coefficient F were excluded. A check for mislabeled gender was performed using Wright's inbreeding coefficient F, calculated from X chromosome data. Annotated females with F close to one or annotated males with F close to zero were excluded. Cryptic relatedness was analyzed using KING software[13] and one sample from each related pair (up to 2nd degree of relatives) was excluded. Furthermore, PCA was performed on 1000 Genomes Project and then used to project and exclude samples with more than 5SD from each of 5 principal components of European population. SNPs with MAF < 1% or with HWE-p within FDR < 5% (based on controls only) were excluded. 137,213 SNPs remained for analysis after QC.

QC for the Replication cohort

QC for the replication cohort included the following steps. Individuals were excluded with less than 95% genotype rate, excess heterozygosity (>3 SD of a larger parent cohort), or with genetic ethnicity or sex inconsistent with self-report. IBD analysis was used to determine unexpected relationships and only one individual included from each 1st degree relative pair. Ancestry outliers with substantial non-European ancestry were identified via EIGENSTRAT (>4SD in top three principal components) and excluded. SNPs were excluded with less than 95% genotyping

rate, Hardy-Weinberg Equilibrium $p<1\times10^{-5}$ in European controls, or $p<1\times10^{-4}$ in African American controls of the larger cohort (based on differing sample sizes and inspection of HWE distributions). SNPs which could not be reliably merged (AT or CG SNPs with 99.99% confidence interval of MAF crossing 50%) were excluded.

QC for the RA cohort

SNPs were excluded with a call rate <0.99 (cases or controls), MAF < 0.01 or if they deviated from Hardy-Weinberg equilibrium (HWE) ($P_{HWE} < 5.7 \times 10^{-7}$). Samples were excluded with a call rate <0.99. Additional QC steps have previously been described.[11]

Statistical and bioinformatic analysis

A logistic regression model with sex and disease duration included as covariates was used to test association between SNPs and CVD in the SLE discovery cohort. For the American-European population sex, disease duration and the first principal component for population stratification were included as covariates. The identification of SNPs associated with CVD in SLE included three steps. First the four CVD variables were tested for association with the Immunochip SNPs using data from the discovery cohort. Next, the top 100 associated SNPs per variable were tested for association with CVD in the SLE replication cohort and SNPs not achieving nominal significance (p>0.05) were excluded. Finally, SNPs with meta-analysis p-values < 0.001 were chosen as candidates for functional follow-up. The identified interleukin 19 (*IL19)* and Signal recognition particle 54 – antisense 1(*SRP54-AS1*) SNPs (n=6) were analyzed in the RA cohort, including sex and disease duration as covariates. In the association analysis of the RA cohort significance was determined as p=0.05. Resulting significant variants (the 3 *IL19* SNPs) were

included in a cross-disease meta-analysis of SLE and RA. In this meta-analysis p-values $<1.0\times10^{-6}$ adjusting for 48,000 independent SNPs on the Immunochip were considered significant. In other analyses p-values <0.05 were considered significant

A logistic regression model with sex and disease duration included as covariates was used to test association between SNPs and CVD in the discovery cohort. For the American-European population sex, disease duration and the first principal component for population stratification were included as covariates. The 6 SNPs in *IL19* and *SRP54-AS1* associated with CVD in SLE were analyzed in the RA cohort using a logistic regression model with sex and disease duration as covariates. Genetic association analysis, meta-analysis, univariate and multivariable regression analysis were performed using PLINK (v1.07)[14] and R.[15] Linkage disequilibrium was determined using rAggr (1000 Genomes, Phase 3, hg19, CEU).[16] Differences between groups were calculated by $\chi2$ test for categorical variables and by Mann-Whitney U test or by Student unpaired *t* test for continuous variables using Statistica 13.2 (Statsoft).

The RegulomeDB (http://www.regulomedb.org/)[17], TRAP web tool (http://trap.molgen.mpg.de/cgi-bin/trap_two_seq_form.cgi)[18], the UCSC Genome Browser (https://genome.ucsc.edu/), ENCODE (https://www.encodeproject.org)[19] and Roadmap Epigenomics Project (http://www.roadmapepigenomics.org)[20] were used to collect information regarding the identified SNPs and to identify possible transcription factors binding at the risk loci. The expression data was obtained from the portal of the Genotype-Tissue Expression (GTEx) Project [9]. The data used for the analyses described in this manuscript were obtained from: the GTEx Portal on 16/05/17.

Functional analysis of variants

Electrophoretic mobility shift assays (EMSA) were performed using LightShift Chemiluminescent EMSA kit (Thermo Scientific), according to the manufacturer's protocol. Probes of 31 bp were designed for the reference and alternative alleles; forward probes were biotin labeled at the 5' end. Probes were annealed (40 fmol) and incubated with nuclear extracts (~10-20 μg) in a binding reaction containing: 1X LightShift Chemiluminescent EMSA binding buffer, 1μg of poly(dI.dC), 7.5% g lycerol, 0.0063% NP-40, 30.1mM KCl, 2mM $MgCl_2$, 0.1 mM EDTA. The reaction was incubated on ice for 40 minutes and run on a 5% TBE Criterion gel (Bio-Rad). Competition was performed with unlabeled probe at 100 X molar excess. Image Lab software (Bio-Rad) was used to visualize and capture images. For nuclear lysate, Jurkat, LCL, K562 and HUVEC cell lines were cultured in RPMI 1640 with 10% fetal calf serum, 2 mM l-glutamine and 100 U/ml penicillin/streptomycin (all GIBCO), at 37° C and 5% carbon dioxide in a humid environment. PBMCs from healthy individuals, recruited at the Department of Clinical Immunology and Transfusion Medicine, Uppsala University Hospital, were prepared by Ficoll-Hypaque (GE Healthcare) density-gradient centrifugation of blood donor buffy coats. Nuclear protein extracts were prepared with NucBuster kit (Novagen) from all cells. An aliquot of Jurkat cells were stimulated with 20 ng/ml phorbol myristyl acetate (PMA) and 20 ng/ml ionomycin for 12 hours and an aliquot of PBMCs were stimulated with interferon-α (500 U/ml) for 20h before extraction of nuclear proteins.

Immunoassays

IL19 in serum was analyzed in 394 SLE patients from Uppsala University hospital and Karolinska University hospital by ELISA (Quantiquine, R&D Systems) according to the manufacturer's instructions and levels within the assay range (31.2 - 2,000 pg/mL) were regarded as detectable.

IL-10 in plasma (EDTA) samples was analyzed in 243 SLE patients from Karolinska University hospital and 288 controls on the MSD V-PLEX™ Human Cytokine 30-plex kit (K15054D; Mesoscale Discovery, Gaithersburg, MD) in collaboration with AstraZeneca. In short the plasma samples were just prior to analysis thawed at room temperature and diluted two-fold in sample Diluent2. The diluted samples were incubated on the MSD plates for two hours at room temperature with shaking. Plates were washed and incubate an additional two hours with detection antibodies (as above). After washing 2x with Read buffer T was added to each well and the plate analyzed in a Sector Imager 6000. Calibrator and plasma samples were analyzed in duplicates. Using the MSD Workbench software the response of the calibrator concentrations were plotted as log signal unit on the vertical (Y) axis versus log concentration on the horizontal (X) axis. A weighted four parameter logistic fit (4PL) equation was used for curve fitting and back calculation of plasma sample concentrations. Concentration of plasma IL10 2 SD above the average of healthy individuals (1.26 pg/mL) was considered elevated.

In the SLE discovery cohort antibodies against cardiolipin (CL, IgG and IgM) and β_2 glycoprotein-I (β_2-GPI, IgG) were analyzed in 781 SLE patients and antibodies against prothrombin (PT, IgG) were analyzed in 494 SLE patients by ELISA (Orgentec, Mainz, Germany)[21]. The cut-off levels corresponded to the 99th percentile of healthy blood donors. In addition, antibodies against cardiolipin (CL, IgM and IgM) and β_2 glycoprotein-I (β_2-GPI, IgG) was measured by fluoroenzyme-immunoassay (Phadia-250 instrument, Thermo-Fisher Scientific

Phadia AB, Uppsala, Sweden) in 171 SLE patients.[22] Lupus anticoagulant (LA) was determined in 311 SLE patients with a modified dilute Russel viper venom method, (Biopool, Umeå, Sweden) using Biocloth lupus anticoagulant. Levels of antibodies against aCL (IgG and IgM) and β_2-GPI (IgG) measured by ELISA (Orgentec) were included in the analysis with the *IL19* risk allele (n=781).

In the SLE replication cohort antibodies against cardiolipin (IgG and IgM) and β_2 glycoprotein-I (IgG and IgM) was determined and lupus anticoagulant was measured using the Russell´s viper venom method (including confirmatory studies) as previously described.[23]

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