both day 14 and day 28 of post induction. Spleen mass were significantly increased in LILRA3 knock-in mice (p<0.001). The proportion of Th2, Tfh, germinal center (GC) B, and plasma B cells were increased in knock-in mice (p<0.01), but not Th17 and regulatory T cells. Concentration of serum anti-
dsDNA IgG was significantly elevated in knock-in mice (p<0.001).

Conclusions Our data indicate that LILRA3 promotes lupus-
like disease probably through the excessive expression of Tfh
cells and GC B cells, subsequently help for the induction and
maintenance of plasma cell differentiation and autoantibody
production.

Funding Source(s): None

239 PATTERNS OF ORGAN INVOLVEMENT IN SLE AND
THEIR OUTCOME: A REAL LIFE EXPERIENCE IN A LUPUS
CLINIC

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Background Systemic lupus erythematosus (SLE) is a multisys-
tem autoimmune disorder predominantly affecting the women
of childbearing age. It often manifests with various constitu-
tional symptoms as well as combination of organ systems
involvement and outcome varies in different population with
available treatment. The present study is to see the patterns of
organ involvement and their outcomes at first 6 months with
standard treatment.

Methods This was a retrospective study done in lupus clinic
of Shaheed Suhrawardy Medical College Hospital, Dhaka,
Bangladesh during 2010 to 2016. Patients were included based
on ACR lupus diagnostic criteria and had received standard
treatment. Outcomes were assessed regularly by clinical fea-
tures, urinalysis and serum creatinine done in the appropriate
treatment. The present study is to see the patterns of organ
involvement and their outcomes at first 6 months with standard
treatment.

Results Among 120 patients, 111 (92.5%) were female, age
ranging from 14 to 57 years with a mean of 26.5±10.68
(SD) year. Median follow up was 1.7 years. The most com-
mon manifestations were fever (70%), joint pain (72.5%),
oral ulceration (49%), alopecia (40%), malar rash (28.3%),
photosensitivity (25.8%) and Raynauds phenomenon (19%).
Commonly involved major organ-systems were renal (40%),
nephritis, proteinuria was present in 100% of cases. The other parameters of renal
involvements were RBC >5/HF and RBC or cellular cast in
37.5%. Serum creatinine was raised in 23 patients (19.17%) with
a mean of 1.68±0.96 mg/dl. Renal biopsy was done in
40 (83.3%) cases. The histology showed class-II in 03 (7.5%),
Class-III in 03 (7.5%), class-IV in 20 (50%) and class-V in 08
(20%) cases. With standard treatment, major reduction of
mean serum creatinine, 24 hours UTP and SLEDWI were
observed in most of the cases at least after 6 months. Total
flare occurred in 31 (25.8%) among them renal flare was in
10 (8.33%) and non-renal flare in 21 (17.5%). Four SLE
patients died during the course of treatment.

Conclusions Renal and central nervous systems are the most
commonly involved major organ systems. The overall outcome
is favorable with standard treatment.

Funding Source(s): None

240 TRANS-ANCESTRAL EXCLUSION MAPPING STRATEGY
PRIORITISES RISK ALLELES AT IKZF3 WITH INCREASED
BIOLOGICAL RELEVANCE

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2King’s College London

Background Pinpointing causal risk alleles, carried on extended
risk haplotypes, at susceptibility loci for common disease is
challenging. We present a novel strategy to prioritise tag-SNPs
at risk loci with the highest likelihood of biological relevance
for laboratory functional studies. This strategy involves trans-
ancestral mapping of risk-haplotypes, MAF-exclusion-mapping
of discordant variants, followed by co-localisation of tag-SNPs
with epigenetic annotation/identification of allele-specific tran-
scription factor (TF) binding sites, using data from public
databases such as RoadMap, ENCODE and HaploRegv4, as a
surrogate for causality.

We illustrate the utility of this approach at the Ikaros zinc
finger TF IKZF3, with a 194 kb associated European (EUR)
SLE haplotype carrying 282 tag-SNPs, extending over multiple
genes from the IKZF3 3 flanking-region into the upstream-
region of ORMDL3.

Methods Align IKZF3 control haplotypes from our large EUR
GWAS and five 1000G super-populations. Compare EUR-Afri-
can MAF to delineate discordant tag-SNPs. Use SLE Immunono-
Chip data to exclude variants exhibiting >3% MAF and not
associated (p>0.05) in African-Americans (AA). Undertake co-
localisation analysis, using multiple tools (Coloc-stats web-
server), to prioritise risk alleles overlapping DNase I hotspots
and chromatin modifications characterising active enhancers
and/or promoters in blood cell-types (RoadMap data). Addi-
tional evidence of potential function was sought for chromatin
looping (3D Genome Browser) and differential TF binding
(HaploRegv4).

Results Trans-ancestral mapping reduced the risk-haploype by
47% to 101 kb and the tag-SNPs by 28% to 140. 26 tag-
SNPs exhibited association in both EUR and AA SLE Immunono-
Chip cohorts. All 26 variants reside in regions of open
chromatin in LCLs. 15 of the tag-SNPs lie within regions
involved in chromatin-looping events, bringing together the
full-length promoter and I1 of a shorter IKZF3 isoform. We
discovered allele-specific binding of Fox family members to
the full-length promoter and I1 of a shorter IKZF3 isoform. We
identified two isoforms of the shorter isoform: rs113730542 and rs112876941.

Conclusions We hypothesise that allele-specific binding of Fox
TFs to risk alleles in the promoter and/or I1 of the shorter
isoform IKZF3 may independently modulate the expression of
both isoforms. Since the shorter isoform lacks the four zinc
fingers responsible for DNA binding of Aiolos (E4–6), the
shorter isoform is unable to directly bind DNA. Heterodimer-
isation between the two isoforms may therefore sequester the
full-length isoform in a biologically inactive form. If Fox TFs
stabilise chromatin loops within IKZF3 in an allele-specific
manner, this may provide a mechanism where risk alleles

influence the activity/availability of IKZF3 and promote autoimmunity.

**Funding Source(s):** Versus Arthritis, formerly Arthritis Research UK project grant (20265)

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**Abstract 241**

**SINGLE CELL GENOMICS OF SELF-REACTIVE B CELLS REVEALS THE EVOLUTION FROM BENIGN TO PATHOGENIC AUTOANTIBODY AND STRATEGIES FOR EARLY DIAGNOSIS AND PERSONALISED TREATMENT**

1Mandeep Singh, 1Katherine Jackson, 1Jing Jing Wang, 1Peter Schrofield, 1Mutt Field, 1Timothy Peters, 1Fabio Luciani, 1Tom Gordon, 1Christopher Goodnow, 1Joanne H Reed.

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Background Autoantibodies appear in the serum years before the development of clinical disease in patients ultimately diagnosed with systemic lupus erythematosus (SLE) or Sjögrens syndrome. The transition from benign to pathogenic autoimmunity is not understood. Anti-IgG rheumatoid factors provide an illuminating example of an autoantibody that persists, on average, more than four years prior to the development of systemic vasculitis and type II cryoglobulinemia. The aim of this study was to identify the pathogenic changes occurring in B cells making rheumatoid factor autoantibody during this transition.

Methods Massively parallel sequencing of peripheral blood B cell receptors (BCR) was combined with mass spectrometry peptide sequencing of serum rheumatoid factor autoantibodies to identify circulating B cells expressing IgM rheumatoid factor factors in 4 patients with SLE or Sjögrens syndrome. In a patient presenting with primary Sjögrens syndrome evolving to cutaneous vasculitis, blood samples before and after transition were subjected to single cell analysis of mRNA, genome methylation, and lymphocyte regulatory genes recurrently mutated in lymphoma and leukemia.

Results Circulating rheumatoid factor B cell clones and their matched serum autoantibodies were identified in 4 patients, 3 of whom, produced the stereotypic Wa-type rheumatoid factor with IGHV1–69 and IGKV3–20 variable domains. Longitudinal analysis of a patient before and after vasculitis revealed a single Wa-type rogue clone was responsible for the rheumatoid factor over a period of 6 years. Compared to the patients normal memory B cells, the rogue cells had aberrant gene expression corresponding to CD11c+CD21 low B cells observed in autoimmunity, and hypomethylation of gene regions aberrantly hypomethylated in chronic lymphocytic leukemia (CLL). A loss-of-function somatic mutation in a Kelch-like protein gene, KLHL6 identical to recurring CLL and lymphoma mutations was acquired by half of the rheumatoid factor B cells. KLHL6 mutant cells slowly accumulated antibody variable domain replacement mutations that did not alter binding affinity but caused IgM-IgG immune complexes to precipitate at temperatures below 25°C.

Conclusions Transition from a benign to pathogenic rheumatoid factor was preceded by a lymphoproliferative disease mutation in the responsible B cells and resulted in accumulation of antibody somatic mutations that diminish immune complex solubility. The ability to detect clones of the rheumatoid factor that are accumulating replacement mutations years prior to the patient developing cryoglobulinemia represents an opportunity to interfere with the conversion from asymptomatic seropositivity to clinical disease.

**Funding Source(s):** Australian National Health and Medical Research Council and New South Wales Department of Health

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**Abstract 242**

**ROLE OF STIGMA AND SOCIAL ISOLATION ON DEPRESSION IN PATIENTS WITH CHRONIC CUTANEOUS LUPUS ERYTHEMATOSUS**

Cristina Drenkard*, Laura Aspey, Gaobin Bao, Charmayne Dunlop-Thomas, S Sam Lim. Emory University

Background Skin disorders can cause mental health problems associated with stigmatization and social isolation. We found that 26% of individuals with chronic cutaneous lupus erythematosus (CCLE) reported moderate to severe depressive symptoms. While patients perceptions of disrespectful office staff increased the risk of depression, emotional support was associated with a reduction. In this study, we examined the relationships between stigma, social isolation, and depression. We further examined if social isolation mediates the relationships between stigma and depression and whether sociodemographic characteristics may moderate those relationships.

Methods We conducted a cross-sectional study in a predominantly African American cohort of patients with primary CCLE from metropolitan Atlanta, Georgia, U.S. Depression, stigma and social isolation were assessed using the NIH PROMIS short forms. Linear and multiple regression were used to examine the relationship between depression, stigma and social isolation. Education attainment, poverty and race were explored as potential moderators.

Results Among 118 patients with a documented diagnosis of primary CCLE, 104 (88%) were female, 96 (81%) were African American, 54 (46.2%) completed high school or less, 40 (40.8%) lived in poverty and 34 (28.8%) self-reported moderate to severe depressive symptoms. While patients perceptions of disrespectful office staff increased the risk of depression, emotional support was associated with a reduction. In this study, we examined the relationships between stigma, social isolation, and depression. We further examined if social isolation mediates the relationships between stigma and depression and whether sociodemographic characteristics may moderate those relationships.

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**Table 1** Multiple linear regression models for predicting depression in CCLE

<table>
<thead>
<tr>
<th>Predictor Variable</th>
<th>Model 1* (Mediator effect of Social Isolation)</th>
<th>Model 2** (Moderator effect of Education)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( \beta )</td>
<td>( p)-value</td>
</tr>
<tr>
<td>Stigma</td>
<td>-0.018</td>
<td>0.88</td>
</tr>
<tr>
<td>Social isolation</td>
<td>0.527</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Education (\text{high school})</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Stigma*Education (\text{high school})</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

*Controlled for age, race, gender and education; **Controlled for age, race and gender.