blood samples for genetic analysis will be stored in the DANBIO-database/Danish Reuma Biobank, in which, since 2000/2015 respectively, collection of information regarding e.g. demographics and disease activity-/tissue samples from patients with inflammatory- and connective tissue disease has taken place. Patients will be matched (gender/age) against participants in the Danish Blood Donor Study in a 1:10 ratio. Sample size to detect degree of synergy between environmental risk behaviour and minor allele frequency of susceptible genes was calculated. Lifestyle and environmental exposures will be collected by self-report and by pulling data from Danish registries. Genetic analysis will be conducted with Illumina sequencing instruments.

Results We identified 966 patients registered in DANBIO with SLE. 20 000 control patients from the Danish Blood Donor Study have completed a self-report questionnaire and genetic sequencing on collected blood samples has been performed. To exemplify the power of this study, we found from the literature risk ratios for developing SLE of about 1.5 for both current smokers and persons with polymorphisms in the signal transducer and activator of transcription 4-gene. By computer modelling we calculated the ability to detect a degree of synergy of 45% with a power of 80%.

Conclusion From this study we expect to provide new information on how certain lifestyle and environmental factors may push the development of SLE in genetically predisposed individuals. Hereby point at new candidate sites of intervention in both treatment and prophylaxis.

This project will have the potential to collaborate with similar upcoming projects in Europe allowing analysis of less prevalent genetic aberrations and/or environmental exposures.

PS2:40 ASSOCIATION OF PEPTIDYLARGININE DEIMINASE (PADI)-4 POLYMORPHISMS WITH SYSTEMIC LUPUS ERYTHEMATOSUS AND LUPUS NEPHRITIS

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Purpose Peptidylarginine deiminase (PAD) 1–4 and PAD6 are responsible for protein citrullination. PAD4 is highly expressed in neutrophils and is essential for NETosis, which has been implicated in the pathogenesis of SLE, especially lupus nephritis (LN). Single nucleotide polymorphisms (SNPs) in PADI4 are responsible for altered stability of PAD4 transcripts, altered functionality of the enzyme and differential expression in neutrophils. We aimed to investigate the risk of SLE and LN conferred by SNPs in PADI4.

Methods 236 SLE patients and 484 healthy controls were genotyped for 9 SNPs in PADI4, to investigate potential associations with occurrence of SLE and LN. Selected SNPs are known to alter functionality and/or expression of the enzyme and/or have previously been associated with other autoimmune diseases, including rheumatoid arthritis. Genotypes were analysed using an in-house multiplex bead-based Luminex assay. All analyses were corrected for age and gender.

Results Compared to homozygous carriage of the major alleles, heterozygous carriage of the minor allele of rs1748033 as well as both heterozygous and homozygous carriage of the minor allele of rs1635564 were associated with increased occurrence of SLE (p=0.02, OR 1.54, 95% CI: 1.07 to 2.22, and p=0.02, OR 1.55, 95% CI: 1.08 to 2.23 and p=0.03, OR 2.06, 95% CI: 1.07 to 3.94, respectively). Additionally, homozygous minor allele carriage of rs1635564 was associated with an increased occurrence of LN (p=0.03, OR 3.35, 95% CI: 1.2 to 10.97) showing a possible additive effect of the number of minor alleles present (table 1).

Carriages of the minor alleles of five other SNPs (rs11203366, rs11203367, rs874881, rs2240340 and rs11203368) were associated with increased occurrence of LN (table 1).

Conclusions Polymorphisms in PADI4 may alter the functionality and/or expression of the enzyme and lead to altered production of NETs, possibly affecting the altered clearance of NETs observed in lupus nephritis, thereby contributing to the pathogenesis of this severe clinical manifestation of SLE. PADI4_rs1635564 could be a potential marker for both SLE and LN.

PS2:41 MICRORNA-155 AND DISEASE ACTIVITY IN SLE PATIENTS

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Background Recent studies are trying to identify aberrant microRNA levels as a diagnostic signature of SLE as well as

Abstract PS2:40 Table 1 Associations between selected polymorphisms in *PADI4* and occurrence of SLE and LN

	SLE (n = 236)						Lupus nephritis (n = 136)					
		pp vs pq			pp vs qq			pp vs pq			pp vs qq	
SNPs	P- value	OR	95% CI	P- value	OR	95% CI	P- value	OR	95% CI	P- value	OR	95% CI
rs74058715	0.94	1.02	0.58-1.77	NA	NA	NA	0.40	0.69	0.29-1.67	NA	NA	NA
rs11203366	0.33	1.20	0.83-1.76	0.68	1.12	0.66-1.88	**0.008**	2.23	1.24-4.06	0.78	0.89	0.39-2.01
rs11203367	0.39	1.18	0.81-1.72	0.64	1.13	0.67-1.9	**0.009**	2.2	1.22-4	0.91	0.96	0.43-2.14
rs874881	0.27	1.24	0.85-1.82	0.89	0.97	0.58-1.6	**0.007**	2.28	1.26-4.19	0.99	1	0.45-2.21
rs2240340	0.45	1.15	0.79-1.68	0.66	1.12	0.66-1.88	**0.005**	2.35	1.3-4.28	0.97	0.99	0.44-2.21
rs1748033	**0.02**	1.54	1.07-2.22	0.58	1.19	0.63-2.19	0.09	1.61	0.92-2.84	0.53	0.73	0.27-1.95
rs11203368	0.86	1.03	0.71-1.5	0.96	1.01	0.6-1.7	**0.03**	1.95	1.09-3.52	0.81	1.11	0.49-2.49
rs2240335	0.08	1.39	0.96-2.01	0.67	1.13	0.64-1.96	0.29	1.37	0.77-2.45	0.85	0.92	0.38-2.21
rs1635564	**0.02**	1.55	1.08-2.23	**0.03**	2.06	1.07-3.94	0.08	1.65	0.94-2.9	**0.03**	3.35	1.2-10.97

p = major allele, q = minor allele

to understand the role of specific microRNAs as biomarkers for disease activity (DA) and progression. Our aim was to evaluate the peripheral blood (PB) expression of miR-155 in SLE patients and to determine its correlation with the DA in the clinical practice.

Materials and methods We studied 40 SLE patients and 32 healthy controls. miR-155 expression levels in whole PB samples were determined by PCR (SYBR Green technology). 2-δδ Ct method was used for analysis. The DA was assessed by SLE DA index (SLEDAI).

Results miR-155 was upregulated in 50.0% of the patients and without difference in its expression levels in 17 (42.5%) of the patients. ROC curve analysis was conducted in order to evaluate the diagnostic accuracy of the PB expression levels of the studied miRNA. AUC for miR-155 was 0.691 (95% CI: 0.566 to 0.817), p=0.005 with 77.5% sensitivity and 50.0% specificity when the RQ cut value was 1.03. Levels of miR-155 correlated with the diagnosis (rs 0,330, p=0,005), with patient's age (rs 0,366, p=0,002) as well as with the presence of secondary Raynaud phenomenon (rs 0,250, p=0,035). There was no correlations with SLEDAI (p=0, 894) nor with the immunological activity according to ANA titer (p=0.399), a-dsDNA (p=0.817), a-Sm (p=0.285), a-b2GPI (p=0.903), a-CL antibodies (p=0.857) and C3 and C4 complement levels (p=0.062 and p=0.550, respectively).

Conclusions We found a dysregulation of miR-155 in SLE which could suggests its role in the disease pathogenesis. There was no correlation between PB levels of miR-155 and DA as a whole as well as with the immunological activity which might reflect the variants of SLE DA in the studied patients, the difference in their genetic background or in the used medications but larger study is needed to confirm these results in the clinical practice.

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PS2:42 UNMETHYLATED CPG-RICH DNA FRAGMENTS ARE ASSOCIATED WITH THE PRESENCE OF LUPUS NEPHRITIS AND INFLUENCE TLR9-MEDIATED RENAL RESPONSE

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Purpose In systemic lupus erythematosus (SLE), lupus nephritis (LN) represents one of the most severe organ complications. LN is associated with persistent inflammation and perpetuated fibroblast activation, both determined by epigenetic mechanisms involving aberrant CpG DNA promoter methylation. During SLE progression, global methylation patterns are commonly lost. CpG DNA promoter methylation patterns are not limited to the kidney, circulating CpG-rich DNA is also detectable in the blood. However, little is known about its specific contribution to determining disease progression. In the kidney, CpG-rich DNA activates TLR9 signalling mechanisms involved in inflammation and fibrogenesis. Based on these observations, we hypothesised that CpG-rich DNA promoter fragments potentially accelerate renal inflammation and fibrogenesis in SLE-associated LN.

Methods First, CPG-rich DNA from blood samples of SLE patients with and without LN were collected. Then, we tested how these DNA promoter fragments influenced the LN phenotype in a TMPD ('pristane')-induced mouse model. The renal response to the administration of either human or synthetic methylated/unmethylated CpG-rich DNA oligodinucleotides (ODN) was observed. Downstream effects of the administration of circulating CpG-rich DNA fragments on TLR9-signalling were analysed in endothelial cell cultures.

Results Circulating CpG-rich DNA promoter fragments are detectable in SLE patients' blood. LN was associated with accumulation of unmethylated CpG-rich DNA promoter fragments, implicating a mechanistic link. In a rodent model of pristane-induced lupus, administration of CpG-rich DNA (isolated from LN patients or synthetic unmethylated CpG-rich DNA ODN) worsened the renal phenotype. TLR9-mediated intrarenal inflammation can be therapeutically targeted by administration of synthetic methylated CpG-rich DNA oligonucleotides, ultimately associated with suppression of TLR9-mediated signalling responses and renal injury in experimental LN.

Conclusions Our results implicate accumulation of unmethylated CpG-rich promoter DNA fragments in LN. Furthermore. these unmethylated CpG-rich promoter DNA fragments causally contribute to TLR9-mediated inflammation and renal fibrogenesis and administration of methylated CpG-rich ODN attenuated intrarenal TLR9-mediated inflammatory signalling responses. Therefore, biomonitoring of CpG-rich promoter DNA fragments and modulation of intrarenal TLR9 signalling might be a promising therapeutical target in LN.

PS2:43 IS LUPUS MORE PREVALENT IN WORLD'S MOST STRESSED COUNTRIES?

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Background A number of studies have implicated psychological stress as a trigger for autoimmune diseases. In a questionnaire study involving 120 lupus patients emotional stress was selected in over 75% cases as a trigger for their disease.[1] The role of stress as a trigger in lupus however is controversial. Here we study whether there is an association between the prevalence of lupus in various countries and their reported stress measures.

Methods We undertook a literature review of the reported prevalence of lupus in various countries across the world. We then recorded the reported stress index in those countries from Bloomberg's study,[2] which utilised seven equally weighted variables: homicide rates, GDP per capita income inequality, corruption perception, unemployment, urban air pollution and life expectancy to rank 74 countries according to stress levels. Pearsons correlation was used to measure association between national stress indices and lupus prevalence

Results Results are presented in graph 1. Prevalence data was only available in the literature for limited countries. Of the countries studied no correlation was found between national stress indices and lupus prevalence (r=−0.028, p-value 0.449).

Conclusion We found no association between a country's prevalence of lupus and the measured stressfulness of its living environment.