(FDR<0.1) between CD6+ and CD4+ T cells, and 15,597 (FDR<0.1) between CD8+ T cells isolated from synovial fluid compared to those from blood. These differential loops overlap many disease associated GWAS loci such as the TNIP1 and STAT7 PsA loci. We identified 121 genotype associated loops, one of which is associated with a risk locus (GSDMB) known to be associated with several autoimmune diseases. Moreover, we found that chromatin conformation correlates strongly with differences in gene expression and chromatin accessibility, particularly with genes related to T cell activation and inflammatory pathways. Next, we compared T cells isolated from blood of PsA patients to controls, but few significant differences were identified (Table 1). Separating the PsA cohort by disease activity and treatment led to the identification of significantly larger differences. We found numerous differentially expressed genes (DEGs) and differential ATAC-seq peaks in patients with or without active disease, and in those receiving or not receiving biological disease-modifying antirheumatic drugs (bDMARD) (Table 1). Furthermore, there were numerous DEGs and differential ATAC-seq peaks in bDMARD responders (n=8) vs non-responders (n=6) (Figure 1, Table 1). DEGs were enriched for pathways involving immune function such as IL-2 and IL-15 signalling. Differential ATAC-seq peaks were enriched for binding sites for transcription factors such as RUNX1, JUN, IRF4 and STAT2. Furthermore, one of the differential ATAC-seq peaks we identified overlapped SNPs in the psoriasis RUNX3 locus.

Table 1. Number of DEGs and differential ATAC-seq peaks in the various comparisons for CD4+ and CD8+ T cells (all FDR<0.1).

<table>
<thead>
<tr>
<th>Comparison</th>
<th>RNA-seq</th>
<th>RNA-seq</th>
<th>ATAC-seq</th>
<th>ATAC-seq</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients vs healthy controls</td>
<td>46</td>
<td>200</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Patients with active disease vs remission</td>
<td>169</td>
<td>36</td>
<td>1675</td>
<td>3</td>
</tr>
<tr>
<td>bDMARD treatment effect in non-active disease</td>
<td>90</td>
<td>13</td>
<td>75</td>
<td>14</td>
</tr>
<tr>
<td>bDMARD treatment effect active disease</td>
<td>967</td>
<td>295</td>
<td>13176</td>
<td>5069</td>
</tr>
<tr>
<td>Remission vs active disease without bDMARD</td>
<td>17</td>
<td>21</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Remission vs active disease treated with bDMARD</td>
<td>1034</td>
<td>374</td>
<td>2559</td>
<td>41</td>
</tr>
</tbody>
</table>

**Results:** Numbers and proportions of CD4+ T-cells did not vary between controls and patients with skin psoriasis or PsA. Furthermore, no differences between controls and patient groups were observed in the proportion of CD4+ T-cell subsets (naive, central memory, effector memory, CD45RA re-expressing effector memory cells). We detected 820 differentially methylated positions (DMPs) affecting 433 genes in CD4+ T-cells from healthy controls when compared to psoriasis and PsA patients. Based on DMP analyses, groups segregated in principal component analysis (PCA) or partial least-squares discriminant analyses (PLS-DA) (Figure 1). Separation in PLS-DA was centrally influenced by two CGs (cg07021052, cg10687131) localized in QDF7 (Growth and Development factor 7), which affects T-cell regulatory factors FOXP3 and CTLA4. GO analysis of genes with at least one DMP in their promoter region delivered enrichment of hypomethylated genes involved in “negative regulation of focal adhesion assembly,” “cell-substrate junction organization” and “regulation of the triglyceride biosynthetic” DNA methylation profiles (855 DMPs affecting 551 genes) distinguished between skin psoriasis and PsA patients; a high proportion of DMPs associated with interferon-regulated genes (68% total: 8.8% type I, 31.9% type II, 23.8% type I and II IFN), GO analysis delivered an enrichment of hypomethylated genes affecting “carboxylic ester hydrolase,” “aikyl or aly group transferase” and “glutathione transferase activity.” Notably, we observed a majority DMPs in IFN-related genes when comparing healthy controls with PsA patients (61.9% total: 9.1% type I, 29.4% type II, 23.8% type I and II IFN) and controls with skin psoriasis patients (62.7% total: 7.7% type I, 31% type II, 24% type I and II IFN). Moreover, DNA methylation calculated for type I and type II IFN-associated genes significantly differed between healthy controls, skin psoriasis and PsA patients.

**Conclusion:** DNA methylation profiles in CD4+ T-cells discriminate between controls, skin psoriasis and PsA. As DNA methylation signatures may predict disease progression from psoriasis to PsA, they may be applied for molecular patient stratification towards future individualized treatment and care.
groups were compared by logistic regression (SPSS, version 28.0.1). HLA PRSs were defined as high in the highest quartile and low in quartile 1-3, and related pathways according to the KEGG, GO and Reactome databases, and

**Methods:**

Objectives: however, been investigated for specific disease manifestations. This has not, profiling through polygenic risk scores has been shown useful to stratify SLE mortality. Genetic contribution to SLE pathogenesis is important, and genetic systemic lupus erythematosus (SLE) and a cause of significant morbidity and

**Background:** Lupus nephritis (LN) is one of the main clinical challenges in systemic lupus erythematosus (SLE) and a cause of significant morbidity and mortality. Genetic contribution to SLE pathogenesis is important, and genetic profiling through polygenic risk scores has been shown useful to stratify SLE patients according to dominating molecular disease mechanism. [1] This has not, however, been investigated for specific disease manifestations.

**Methods:** Female patients with SLE (n = 1248) and healthy control individuals (n = 519) were genotyped using Illumina’s Global Screening Array. Two PRSs were calculated,[2], one including 20 GWS risk loci for SLE in genes assigned to B-cell related pathways according to the KEGG, GO and Reactome databases, and one including a subset of 12 of these genes limited to B-cell activation pathways. PRSs were defined as high in the highest quartile and low in quartile 1-3, and groups were compared by logistic regression (SPSS, version 28.0.1). HLA variants HLA-DRB1*03:01 and HLA-DRB1*15:01, with in patients with HLA risk serotypes HLA-DRB1*03:01 and HLA-DRB1*15:01, with the highest prevalence of dsDNA antibodies (87 %) demonstrated in patients with HLA-DRB1*03:15 +/- combined with a high SLE B cell PRS (OR 1.84 (1.06-2.54), p = 0.028, for high vs low PRS), Figure 1. Anti-dsDNA antibodies were associated with a higher prevalence of class III or IV nephrits (OR 4.66 (2.78-7.80), p=5.2×10^-9) and the prevalence of nephrits according to the ACR-82 criteria was higher in patients with a high compared to patients with a low B cell activation PRS (OR 1.32 (1.00-1.74), p = 0.048). Numerically, a higher prevalence of nephrits (ACR-82) was observed for patients with a high compared with a low SLE B cell PRS, but the difference was not statistically significant (OR 1.20 (0.91-1.59), p = 0.19).

**Conclusion:** High genetic burden related to B cell function is associated with dsDNA antibody development and LN. Assessing B cell PRSs may be important in order to determine immunologic pathways influencing SLE and to predict clinical phenotype.

**REFERENCES:**


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**Keywords:** Autoantibodies, Genetics/Epigenetics, Systemic lupus erythematosus

**Keywords:** Genetics/Epigenetics, -omics, Vasculitis

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**Background:** Lupus nephritis (LN) is one of the main clinical challenges in systemic lupus erythematosus (SLE) and a cause of significant morbidity and mortality. Genetic contribution to SLE pathogenesis is important, and genetic profiling through polygenic risk scores has been shown useful to stratify SLE patients according to dominating molecular disease mechanism.[1] This has not, however, been investigated for specific disease manifestations.

**Objectives:** In this work, we aimed to investigate associations between B cell polygenic risk scores (PRSs) and disease manifestations in SLE.

**Methods:** Female patients with SLE (n = 1248) and healthy control individuals (n = 519) were genotyped using Illumina’s Global Screening Array. Two PRSs were calculated[2], one including 20 GWS risk loci for SLE in genes assigned to B-cell related pathways according to the KEGG, GO and Reactome databases, and one including a subset of 12 of these genes limited to B-cell activation pathways. PRSs were defined as high in the highest quartile and low in quartile 1-3, and groups were compared by logistic regression (SPSS, version 28.0.1). HLA variants HLA-DRB1*03:01 and HLA-DRB1*15:01, with in patients with HLA risk serotypes HLA-DRB1*03:01 and HLA-DRB1*15:01, with the highest prevalence of dsDNA antibodies (87 %) demonstrated in patients with HLA-DRB1*03:15 +/- combined with a high SLE B cell PRS (OR 1.84 (1.06-2.54), p = 0.028, for high vs low PRS), Figure 1. Anti-dsDNA antibodies were associated with a higher prevalence of class III or IV nephrits (OR 4.66 (2.78-7.80), p=5.2×10^-9) and the prevalence of nephrits according to the ACR-82 criteria was higher in patients with a high compared to patients with a low B cell activation PRS (OR 1.32 (1.00-1.74), p = 0.048). Numerically, a higher prevalence of nephrits (ACR-82) was observed for patients with a high compared with a low SLE B cell PRS, but the difference was not statistically significant (OR 1.20 (0.91-1.59), p = 0.19).

**Conclusion:** High genetic burden related to B cell function is associated with dsDNA antibody development and LN. Assessing B cell PRSs may be important in order to determine immunologic pathways influencing SLE and to predict clinical phenotype.

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