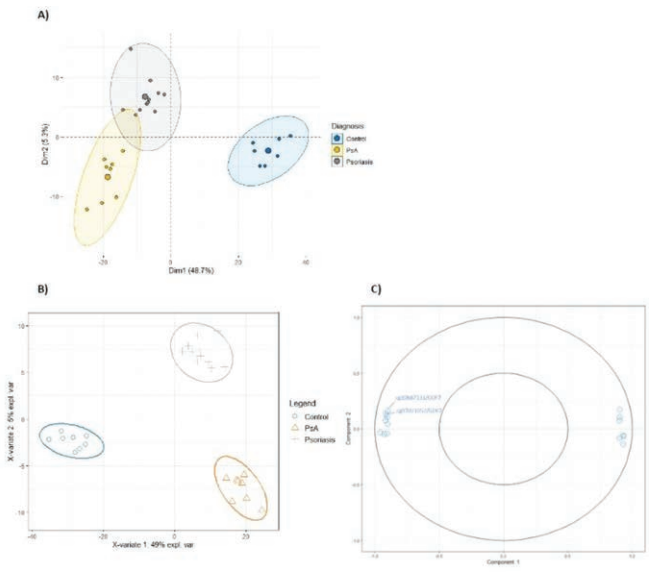


**Figure 1: DNA methylation signatures differentiate healthy controls from skin psoriasis and PsA.** A) Unsupervised Principal Component Analysis (PCA) of 820 Differentially Methylated Positions (DMP) (FDR p-value: <0.05, $|\Delta\beta|>0.1$) discriminates between healthy controls, skin psoriasis, and PsA patients. B) Supervised Partial Least-Squares Discriminant Analysis (PLS-DA) of the same 820 DMPs (FDR p-value <0.05, $|\Delta\beta|>0.1$) even more clearly separates healthy controls from skin psoriasis and PsA patients. C) Correlation circle plot displaying the 15 DMPs (correlation cutoff 0.9) that primarily contribute to the definition of each component of the PLS-DA. DMPs at cg07021052 and cg10687131 are localized in *GDF7* which affects T-cell regulatory factors FOXP3 and CTLA4.

**REFERENCES: NIL.**
**Acknowledgements: NIL.**
**Disclosure of Interests: None Declared.**
**DOI:** 10.1136/annrheumdis-2023-eular.4069

## OP0101 B CELL POLYGENIC RISK SCORES ASSOCIATED WITH ANTI-DSDNA ANTIBODIES AND NEPHRITIS IN SYSTEMIC LUPUS ERYTHEMATOSUS

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

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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 28.0.1.0). HLA variants HLA-DRB1*03:01 and HLA-DRB1*15:01 were assessed in patients using tag SNPs. A p-value < 0.05 was considered significant.
**Results:** SLE was more prevalent in individuals with high compared with a low SLE B cell PRS (OR 1.84 (1.42-2.38), p=$4.0\times10^{-6}$) and mean PRS was higher in cases than controls, 2.92 (2.88-2.96) for cases and 2.68 (2.63-2.74) for controls, p = $4.1\times10^{-11}$). Immunologic disorder (ACR -82) and dsDNA antibodies were more prevalent among patients with a high compared with a low SLE B cell PRS (OR 1.44 (1.08-1.93), p=$1.4\times10^{-2}$, and OR 1.47 (1.07-2.01), p=$1.8\times10^{-2}$, for immunologic disorder and dsDNA antibodies, respectively). Also, effect sizes were augmented 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 1.64 (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 nephritis (OR 4.66 (2.78-7.80), p=$5.2\times10^{-9}$) and the prevalence of nephritis 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 nephritis (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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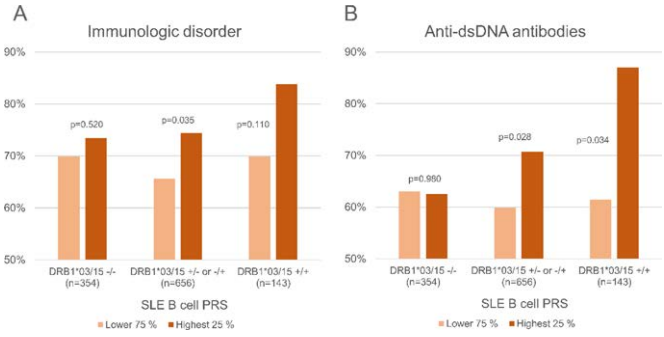


**Figure 1.** Associations with SLE B cell PRS, immunologic disorder (ACR-82) and anti-dsDNA antibodies in HLA subgroups. Female patients with SLE were stratified into three groups according to HLA-type (positive for HLA-DRB1*03:01 or HLA-DRB1*15:01 (DRB1*03/15 +/- or -/+), positive for both (DRB1*03/15 +/+) or negative for both (DRB1*03/15 -/-) risk variants). Each group was then divided into two groups based on the patients' SLE B cell PRSs (highest quartile or quartile 1-3). Prevalence of immunologic disorder according to the ACR -82 criteria (A) and prevalence of dsDNA antibodies (B) was then calculated for all 6 groups.

ACR, American College of Rheumatology; dsDNA, double-stranded DNA; HLA, human leukocyte antigen; SLE, systemic lupus erythematosus; SNP, single nucleotide polymorphism; PRS, polygenic risk score.

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**Disclosure of Interests: None Declared.**
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## OP0102 IDENTIFICATION OF NEW RISK LOCI AND PATHWAYS INVOLVED IN GCA PATHOGENESIS BY A GENOME-WIDE STUDY

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

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**Background:** Giant cell arteritis (GCA) is a chronic large-vessel vasculitis that affects mainly the aorta and its primary branches, and in Western countries is the most common form of vasculitis in people older than 50 years. The most severe manifestations of GCA include blindness and ischemic stroke caused by occlusion of affected arteries. GCA presents a complex aetiology whose genetic component remains largely unknown. Currently, options for both diagnosis and treatment for this pathology are limited, highlighting the need to better understand the genetic factors involved in susceptibility to GCA.

**Objectives:** The main goal of this study was to characterise the genetic basis of GCA by performing the largest genome-wide association study (GWAS) in this vasculitis to date.

**Methods:** A total of 3,498 GCA patients with GCA and 15,550 healthy individuals from ten populations of European ancestry were included in this study. After strict quality controls and imputation, 6,691,294 genetic variants were analysed by logistic regression using the first 10 principal components and sex as covariates. Loci showing a significant (p<5E-8) or suggestive (p<5E-5) association with the disease were selected for functional *in silico* analyses, including causal gene prioritisation with FUMA, enrichment of functional annotations of cell-specific histone marks using GoShifter. Finally, we performed a drug repurposing analysis, by evaluating the proposed mapped genes of the significant loci as targets for approved drug using the DrugBank database, and developed a polygenic risk score (PRS) for GCA susceptibility prediction.

**Results:** Three risk loci for GCA not previously reported were identified, two of them located in genes related to the vascular endothelial growth factor (VEGF) pathway: *MFGE8* (rs8029053, p=4.96E-8, OR=1.19), encoding lactadherin, and *VTN* (rs704, p=2.75E-9, OR=0.84)], encoding vitronectin; and the third one located in the gene *CCDC25* (rs11782624, p=1.28E-8, OR=1,18), that codifies a receptor of neutrophil extracellular traps (NETs). Additionally, we replicated the associations previously described within the HLA region and the *PLG* gene, which is also involved in angiogenesis. The results of the functional annotation showed that the GCA-associated loci act as regulatory variants influencing gene expression in vascular tissue and immune cell types. Furthermore, we also found a significant enrichment in histone marks in several immune cell types, especially in natural killer cells. The results of the drug repurposing analysis suggest abciximab, an antagonist of the vitronectin protein and approved for the treatment of acute coronary syndrome, as a potential candidate to treat GCA. Finally, the PRS model was best defined by including 28 genetic variants, being capable of identifying a fraction of individuals with more than three times the risk of developing GCA (OR=3.1 [2.1-4.7], p=1.71E-8).

**Conclusion:** Through the largest genomic study performed in GCA to date, we identified three genetic regions associated with this vasculitis that were not previously reported. These results also identified new physiological pathways and cell types potentially relevant to the development of the disease. These results allowed us to establish a prediction tool for identifying individuals at high-risk for developing GCA and also to propose further investigation of abciximab, a drug that could be potentially repurposed for treatment of GCA.

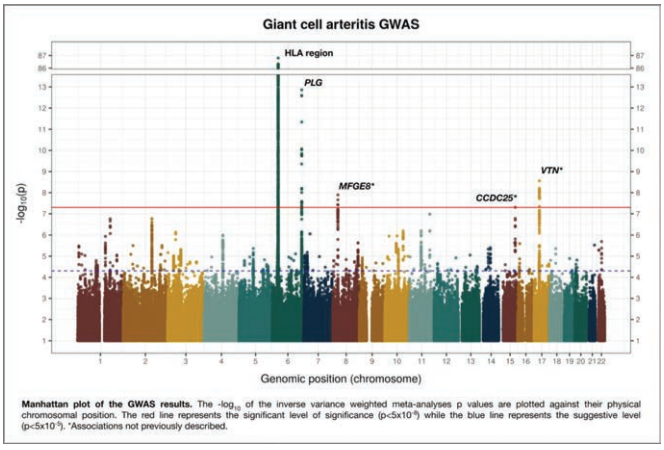


**Figure 1.**

**REFERENCES: NIL.**

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**Disclosure of Interests: None Declared.**

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OP0103

## ANALYSIS OF PROTEIN QUANTITATIVE TRAIL LOCI TO IDENTIFY GENETIC BIOMARKERS OF TREATMENT RESPONSE TO ETANERCEPT IN PATIENTS WITH RHEUMATOID ARTHRITIS

**Keywords:** Genetics/Epigenetics, -omics, Rheumatoid arthritis

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**Background:** Treatment response to etanercept in patients with rheumatoid arthritis (RA) is heterogeneous, with up to 40% switching due to failure/ineffectiveness[1]. There are no validated pre-treatment biomarkers of response. Due to