POS0351 **A DEEP LEARNING METHOD UNCOVERS NOVEL PATHWAY ASSOCIATIONS IN SYSTEMIC LUPUS ERYTHEMATOSUS**

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Background: While there have been recent improvements in therapy for systemic lupus erythematosus (SLE), unmet need remains for novel, efficacious treatments. Artificial intelligence can facilitate drug discovery by identifying potential target molecules and pathways.

Objectives: To devise a Deep Learning method that ranks genes and pathways differentially expressed in SLE by an integrated metric of expression and interactivity.

Methods: HT2A array expression data (17,799 transcripts) were obtained from whole blood samples taken at baseline (N=1,760) from patients with SLE enrolled in two phase 3 trials (NCT01196091 and NCT01205438). We applied a Deep learning algorithm¹ to create a disease-specific gene network for SLE from the Decagon and MetaCore molecular interaction databases^{2,3}. A meta-analysis was conducted for each candidate gene by calculating its distance from other genes in the disease-specific network (interactivity analyses). The distance was then multiplied by each gene's utility score, a measure of the gene's relevance to SLE disease activity derived from public datasets^{4,5}. The final output was the fractional rank (0–1) of utilities⁵ for each gene against prespecified outcomes of SLEDAI-2K and IFN gene signatures, analyzed as a continuous variable combining 34 IFN-related genes. Selected JAK-STAT, cytokine, and IFN genes are presented. Pathways enriched in the top 250 genes from the input data and Deep Learning output were analyzed by hypergeometric tests.

Results: The highest-ranked gene for SLEDAI-2K and IFN signature status was IFN γ , followed, as expected, by the IFN α gene family (Table 1). Application of the Deep Learning method markedly affected pathway analysis outcomes, revealing strong associations in pathways including those related to CD4+ T cell differentiation as well as macrophage and dendritic cells, which were not apparent in conventional analysis (Figure 1).

Table 1.

Gene	SLEDAI-2K fractional rank	IFN signature fractional rank
IFN γ	0.9999	0.9999
IFN α †	0.999*	0.999*
STAT1	0.9991	0.9991
IL10	0.9990	0.9987
IFNB1	0.9990	0.9989
STAT6	0.9981	0.9966
IL6	0.9974	0.9973
STAT4	0.9959	0.9944
IL12A	0.9952	0.9932
IL12B	0.9950	0.9938
STAT5A	0.9929	0.9940
STAT3	0.9915	0.9930
IFN γ R2	0.9829	0.9770
IFN γ R1	0.9812	0.9840
IL23A	0.9806	0.9895
IL10RA	0.9805	0.9816
IL6ST	0.9791	0.9695
STAT2	0.9772	0.9914

†IFN α genes were similarly ranked.*Range: 0.9988–0.9999*0.9991" denotes that the SLEDAI-2K rank for STAT1 is higher than 99.91% of the whole genome.

Conclusion: Deep learning algorithms incorporating interactivity analyses revealed disease associations in SLE that were not apparent when using conventional bioinformatic approaches.

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Heatmap summarizing enriched pathways from the top 250 analyzed genes

The heatmap's color intensity corresponds to the $-\log_{10}$ FDR-adjusted p value. The dendrogram shows groups of pathways with similar behavior.

Figure 1.

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POS0352 **ALLELIC VARIANTS IN THE ABCG2 GENE CAN LEAD TO HYPERURICEMIA AND GOUT**

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Background: The level of uric acid is largely determined by the functions of urate transporters, which are located in the kidney and intestine. The ABCG2 protein is the major excretor of uric acid and its dysfunction may lead to the development of hyperuricemia and gout.

Objectives: The aim of our study was to detect the occurrence and frequency of allelic variants in the ABCG2 gene that can lead to impaired function of the ABCG2 protein and to the development of hyperuricemia and gout.

Methods: We examined allelic variants of ABCG2 using PCR amplification and Sanger sequencing of all coding regions and exon-intron boundaries in 359 patients with primary hyperuricemia and gout.

Results: We found a rare in-frame deletion p.K360del and 15 missense variants, two of which were common (p.V12M, p.Q141K) and 13 were very rare (p.M71V, p.G74D, p.M131I, p.R147W, p.T153M, p.I242T, p.R236X, p.F373C, p.T421A, p.T434M, p.S476P, p.S572R, p.D620N). The p.R236X variant leads to a premature stop codon. The p.V12M variant probably has a protective effect against gout (minor allele frequency – MAF – in our cohort = 0,025 / MAF in the European population = 0,061), while the p.Q141K variant increases the risk of gout (MAF in our cohort = 0,213 / MAF in the European population = 0,094) (1). As for the rare variants, the p.R147W, p.T153M, p.F373C, p.T434M, p.S476P and p.S572R

according to functional analyzes reduce the function of the ABCG2 protein (2). Based on *in silico* prediction, the impact on reduced function is expected for variants p.M71V, p.G74D, p.M131I, p.R147W, p.I242T, p.F373C, p.T434M, p.S476P and p.S572R.

Conclusion: Our data suggest that the common variant p.Q141K and most of the rare variants in the ABCG2 gene affect the function of the ABCG2 urate transporter and are a genetic risk factor for hyperuricemia and gout.

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POS0353 DEEP PHENOTYPING OF PSORIASIS BASED ON LIPID METABOLISM RELATED GENES BY INTEGRATIVE SYSTEMS ANALYSIS

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Background: Psoriasis is an immune-mediated inflammatory, genetic disease with numerous concomitant metabolic disorders¹. Patients with psoriasis experience substantial morbidity and increased rates of cardiometabolic diseases². Among the metabolic disorders, lipid disturbances are recognized as a very important part in the pathogenesis of psoriasis and psoriasis-associated cardiometabolic diseases^{3,4}.

Objectives: To characterize the molecular features of psoriasis by the development of a classification system that was based on the gene expression profile of lipid metabolism related genes.

Methods: We performed molecular subtyping and association analysis of psoriasis from Gene Expression Omnibus (GEO). The training sets includes GSE13355 cohort (N = 58), GSE14905 (N = 28) cohort and GSE30999 cohort (N = 81), while the GSE54456 (N = 92) was selected as the validation set. Energy metabolism-related genes were collected from MSigDB (version 7.0; <http://software.broadinstitute.org/gsea/msigdb/>). Based on these psoriasis lipid metabolism-related genes, we conducted consensus molecular subtyping with nonnegative matrix factorization (NMF). Finally, Gene set variation analysis (GSVA) was used to score individual subtypes against the metabolism-related gene sets, and each group got a GSVA index.

Results: Total 104 lipid metabolism-related genes were clustered into three subgroups (Figure 1A). GSVA revealed the lipid metabolism with the correlation in subtypes. There was no statistical difference was identified between the subtype 1 and subtype 2 ($P > 0.05$, Figure 1B), so we merged the two types as a new Sub1, another subtype was named as the new Sub2 (Figure 1C). We finally identified 2 distinct subtypes of psoriasis in GEO cohort that were characterized by significantly different lipid metabolic gene score. Sub1 was featured by higher metabolic gene score compared with that of Sub2 ($P < 0.001$; Figure 1D). The lipid metabolic subtype classification was successfully validated in another independent patient cohorts (GSE54456).

Conclusion: This study established a new classification based on the gene expression profiles of lipid metabolic genes, thereby furthering the understanding of the pathogenesis and psoriasis-associated diseases.

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Figure 1: Molecular typing of patients with psoriasis based on lipid metabolism-related gene expression profiles. (A, C) consensus clustering of 167 GEO samples by NMF, a heatmap displaying the expression pattern of the lipid metabolism related subtypes is shown. (B) comparison of lipid metabolic score levels among three subgroups. (D) comparison of lipid metabolic score levels between the final two subgroups. $^{\circ}P > 0.05$; $^{***}P < 0.001$.

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POS0354 DETECTION OF ABCG2 VARIANTS IN ENCODING OF URATE TRANSPORTERS ASSOCIATED WITH THE HYPERURICEMIA IN HAEMODIALYSIS PATIENTS

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Background: Hyperuricemia is associated with gout, hypertension, cardiovascular diseases and renal disease. The presence of chronic kidney disease (CKD) is associated with low excretion of the uric acid as the homeostasis in maintaining of serum levels of uric acid is impaired. Progression of CKD is connected to hyperuricemia and lowering levels of the uric acid is one of the most important goals in clinical treatment. Dysfunctional variants of ATP-binding cassette transporter subfamily G member 2 (ABCG2), a major urate transporter in the kidney and intestine, are the major causes of hyperuricemia and gout.

A recent studies found that ABCG2 is also a major transporter of uremic toxins and ABCG2 dysfunctional variants are risk genetics factors for mortality in hemodialysis patients.

Objectives: The aim of the present study was to investigate the frequencies of ABCG2 variants in cohort of hemodialysis patients.

Methods: In this retrospective one centre study 167 patients (age=79.8±11.03; female=74) with end-stage CKD (pre-dialysis n=86; dialysis n=79) were collected. Peak urate levels were 456.3±113.6 µmol/l in pre-dialysis and 572.93±114.56 µmol/l in dialysis. ABCG2 coding regions were analyzed from genomic DNA, as we described previously (1). The reference sequence was defined as version ENST00000237612.7; the reference protein sequence was defined as Q9UNQ0. The chi-square goodness-of-fit test was used to compare minor allele frequencies (MAF), and the log-rank test was used to compare empirical distribution functions.

Results: In the CKD cohort, 15 intronic and seven non-synonymous allelic exonic variants were detected: two common (rs2231137/p.V12M; rs2231142/p.Q141K), five ultra rare and/or rare (rs142634180/p.R45Q, rs759726272/p.M131I, rs140207606/p.R236X, rs138606116/p.G354R, rs138892154/p.A607V), and one novel (p.E344D). Common variant p.V12M, previously reported as protective