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THU0019 **INTRON REGIONS OF PIK3AP1 (BCAP) AND SPON2 (SPONDIN-2) GENES ARE DIFFERENTIALLY METHYLATED IN PATIENTS WITH PERIODIC FEVER, APHTHOUS STOMATITIS, PHARYNGITIS AND ADENITIS (PFAPA) SYNDROME**

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Background: Periodic fever, aphthous stomatitis, pharyngitis and adenitis (PFAPA) syndrome is the most common autoinflammatory disease in children, often grouped together with hereditary periodic fever syndromes, although its cause and hereditary nature remain unexplained.

Objectives: We investigated whether a differential DNA methylation was present in DNA from peripheral blood mononuclear cells (PBMC) in patients with PFAPA versus a group of healthy young individuals.

Methods: A whole epigenome analysis (MeDIP and MBD) was performed using pooled DNA libraries enriched for methylated genomic regions. Of identified candidate genes, two with most significantly different methylation levels were further evaluated with methylation specific restriction enzymes coupled with qPCR (MSRE-qPCR).

Results: The analysis showed that PIK3AP1 and SPON2 intronic gene regions are differentially methylated in patients with PFAPA. MSRE-qPCR proved as a quick, reliable and cost-effective method to confirm results from MeDIP and MBD.

Conclusion: Our findings indicate that B cell adapter protein (BCAP) as PI3K binding inhibitor of inflammation and spondin-2 (SPON2) as a pattern recognition molecule and integrin ligand could play a role in etiology of PFAPA. Their role and impact of changed DNA methylation in PFAPA etiology and autoinflammation need further investigation.

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THU0020 **NO CAUSAL ASSOCIATION OF SERUM URATE OR GOUT WITH ALZHEIMER'S DISEASE: A MENDELIAN RANDOMIZATION ANALYSIS**

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Background: Several epidemiologic studies have found a lower risk of Alzheimer's disease (AD) among individuals with a history of gout¹ or high serum urate levels², which are the precursor to gout. Serum urate may have neuroprotective benefits for AD, however it is possible that reverse causation and residual confounding could explain the observational evidence.

Objectives: To study the causal associations of serum urate and gout with Alzheimer's disease using Mendelian Randomization (MR) methods.

Methods: Two-sample MR was performed to examine the causality of: 1) serum urate on Alzheimer's disease and 2) gout on Alzheimer's disease. Single nucleotide polymorphisms (SNP) identified from a genome-wide association study

of 457,690 adults described 183 SNPs associated with serum urate and gout, which were used as instrumental variables³. Additional single-SNP analyses were conducted using SNPs from three genes identified as major determinants of urate levels (SLC2A9, SLC22A12, and ABCG2). SNPs for AD came from the International Genomics of Alzheimer's Project, comprised of 35,274 AD cases and 59,163 cognitively normal elderly controls⁴. Inverse-variance weighted (IVW) models were the primary method used to examine the associations between each exposure and risk of AD. Additional analyses examined the potential impact of pleiotropy via MR-Egger models. Single-SNP analyses used the Wald ratio. All analyses were performed using R.

Results: There was no evidence of a causal association between genetically-determined serum urate or gout and risk of AD from IVW analyses (both p>0.1) (Table 1). MR-Egger analyses yielded similar estimates (both p>0.1) and the intercepts of the MR-Egger regressions did not suggest the presence of directional pleiotropy (p=0.64 for serum urate exposure and p=0.98 for gout exposure) (Table 1). Additionally, none of the three individual SNPs were significantly associated with risk of AD (all p>0.05) (Table 2).

Table 1. Association of combined SNPs for serum urate and gout with Alzheimer's disease

	Number of SNPs	OR	95% CI	p value	MR-Egger intercept (p value)
Serum urate exposure (per 1 mg/dL increase)					
IVW	158	1.04	0.98-1.11	0.187	
MR-Egger	158	1.06	0.96-1.17	0.228	-0.001 (0.645)
Gout exposure (gout vs. non-gout)					
IVW	158	1.03	0.99-1.06	0.161	
MR-Egger	158	1.03	0.98-1.07	0.290	5.477 (0.976)

Table 2. Association of individual SNPs for serum urate and gout with Alzheimer's disease

Gene	SNP	OR	95% CI	p-value
Serum urate exposure (per 1 mg/dL increase)				
SLC2A9	rs3775947	1.12	1.00-1.26	0.059
SLC22A12	rs531763	0.92	0.71-1.20	0.545
ABCG2	rs74904971	1.22	0.99-1.50	0.059
Gout exposure (gout vs. non-gout)				
SLC2A9	rs3775947	1.08	1.00-1.17	0.059
SLC22A12	rs531763	0.94	0.77-1.15	0.545
ABCG2	rs74904971	1.06	1.00-1.13	0.059

Conclusion: Using both serum urate and gout as instrumental variables in MR analysis, these findings suggest that serum urate and gout are not causal determinants for the development of AD. The inverse associations described in observational studies may in part be due to confounding or reverse causality.

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THU0021 **IDENTIFICATION OF MUSCLE ASSOCIATED KEY GENES TO SUPPORT AXIAL SPONDYLOARTHRITIS DIAGNOSIS BY TRANSCRIPTOMIC APPROACH, THE MYOSPA STUDY**

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Background: Early diagnosis of axial Spondyloarthritis (axSpA) represents a major clinical challenge nowadays. Increasing evidence has determined that early diagnosis, prompt treatment initiation and early achievement of remission are the best predictors of long-term clinical, functional and radiographic outcomes. New tools to support the diagnosis are needed.

Objectives: This study aims to identify differentially expressed genes that may improve the current clinical diagnosis approach for early axSpA.

Methods: A cross-sectional study was conducted on 50 participants, 25 patients with axSpA (according to ASAS criteria) and 25 Healthy Controls, matched by gender, age and levels of physical activity. Peripheral blood samples were collected and RNA-Seq technology was performed. Normalization of raw data, and identification of differentially expressed genes was obtained using edgeR and limma-voom R packages. Gene Set Enrichment Analysis (GSEA) and Functional Enrichment analysis using Gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) annotations were also performed. A number of Differently Expressed Genes were highlighted.

Results: 311 genes were identified as being significantly differentially expressed between patients and controls. In details, 129 downregulated (7 genes have fold change more than 1) and 182 upregulated genes (3 genes have fold change more than 1) are highlighted. These genes are mostly involved in Myogenesis, Innate Immune Signalling and JAK/STAT pathways. Several genes with functions of skeletal muscle development and muscle contraction were identified.

Conclusion: The evidence disclosed that regulation of muscle development and contraction may be also engaged in physiopathology mechanisms of axSpA. These new cues open new perspectives for diagnosis and therapeutic approaches in axSpA.

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THU0022 DIFFERENTIAL DNA METHYLATION AS A PREDICTOR OF TOCILIZUMAB RESPONSE IN RHEUMATOID ARTHRITIS PATIENTS

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Background: Tocilizumab (TCZ) is a biological disease-modifying antirheumatic drug that blocks IL-6 signalling and is effective in ameliorating disease activity in rheumatoid arthritis (RA). However, approximately 50% of patients do not respond adequately to TCZ and some patients report adverse events. Considering there is growing evidence that DNA methylation is implicated in RA susceptibility and response to some biologics (1, 2), we investigated DNA methylation as a candidate biomarker for response to TCZ in RA.

Objectives: To identify differential DNA methylation signatures in whole blood associated with TCZ response in patients with RA.

Methods: Epigenome-wide DNA methylation patterns were measured using the Infinium EPIC BeadChip (Illumina) in whole blood-derived DNA samples from patients with RA. DNA was extracted from blood samples taken pre-treatment and following 3 months on therapy, and response was determined at 6 months using the Clinical Disease Activity Index (CDAI). Patients who had good response (n=10) or poor response (n=10) to TCZ by 6 months were selected. Samples from secondary poor responders (n=10) (patients who had an improvement of CDAI and were in remission at 3 months, followed by a worsening of CDAI at 6 months) were also analysed. Differentially methylated positions and regions (DMPs/DMRs) were identified using linear regression, adjusting for gender, age, cell composition, smoking status, and glucocorticoid use. Gene Set Enrichment Analysis (GSEA) was used to identify significant pathways associated with

response and Functional Epigenetic Module analysis of interactome hotspots in regions of differential methylation.

Results: 20 DMPs were significantly associated with response status at 6 months in the pre-treatment samples. Another 21 DMPs were associated with response in the 3 month samples. Within good responders, 10 DMPs showed significant change in methylation level between pre-treatment and the 3 month samples (unadjusted P-value <10⁻⁶). One DMP, cg03121467, was significantly less methylated in good responders compared to poor responders in the pre-treatment samples. This DMP is close to *EPB41L4A* and thought to have a role in β -catenin signalling. GSEA of DMRs in non- and secondary non- responders identified histone acetyltransferase pathways and included the *KAT2A* gene, which is a repressor of NF- κ B. Additional analysis of interaction hotspots of differential methylation identified significant interactions with *STAMBP* and *PTPN12* associated with response status.

Conclusion: These preliminary results provide evidence that DNA methylation patterns may predict response to TCZ. Validation of these findings in other larger data sets is required.

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THU0023 DETAILED PROFILE OF CO-OCCURRENCE OF RELAPSING POLYCHONDRIITIS AND AUTOIMMUNE THYROID DISEASE

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Background: Relapsing polychondritis (RP) is a rare inflammatory disease, which is characterized by recurrent inflammation and destruction of cartilage tissues. RP also has the profile of autoimmune disease and is often complicated with other autoimmune disease. Autoimmune thyroid disease (AITD) is one of common autoimmune diseases, which consists of Graves' disease (GD) and Hashimoto's thyroiditis (HT). While RP is reported to be complicated with AITD¹, there has been no study on detailed profile of co-occurrence of RP and AITD.

Objectives: We aimed to reveal whether there is common (statistically significant) co-occurrence of RP and AITD. We also analyzed clinical and genetic profiles characterizing the co-occurrence.

Methods: We recruited 117 patients with RP and checked their medical records in order to obtain the information about compilation of AITD and clinical features. In addition, we genotyped Human Leucocyte Antigen (HLA) A, B Cw, DRB1, DQB1 and DPB1 alleles for 88 of the 117 patients. Co-occurrence ratio was compared with prevalence of AITD in the Japanese population. Associations of co-occurrence of AITD with clinical manifestations or HLA alleles were analyzed among the patients.