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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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