

## Abstract

Primary hyperuricemia, as a condition of elevated serum uric acid levels, is caused by various factors and necessarily precedes a form of inflammatory arthritis referred to as gout. Uric acid is the end product of purine catabolism and requires specialized proteins for its transport. Pathogenic variants in the genes for these transport proteins can have a major negative impact on their function, thereby affecting the resulting serum uric acid levels. However, chronically elevated uric acid levels are not the only predisposition to the development of gout. Other factors, such as epigenetic mechanisms or genetic predispositions to inflammatory conditions caused by immune dysregulation, are likely to play a role in disease progression.

The aim of the study was to analyse damaging variants in genes for important urate transporters *ABCG2*, *SLC22A12* and *SLC2A9*, which may cause impaired excretion or reabsorption of uric acid and thus contribute to the development of primary hyperuricemia and gout, or rare hereditary renal hypouricemia. We also focused on circulating miRNAs in the plasma of patients with primary hyperuricemia, gout and gout attack.

We identified and functionally characterized over ten rare nonsynonymous variants in the *ABCG2* gene. Most of these variants had a negative impact on protein expression, localization or function. Furthermore, in a cohort of patients with primary hyperuricemia and gout, we confirmed the importance of the frequently occurring risk variant p.Q141K, and our results showed that the presence of the variant outweighed several other risk factors (age, overweight, higher C-reactive protein levels) associated with hyperuricemia and gout.

We found synonymous and intronic variants in the *SLC22A12* and *SLC2A9* genes associated with hyperuricemia and gout. We discovered and functionally described a novel causal variant for renal hypouricemia type 1 in the *SLC22A12* gene. In a cohort of Roma patients and their family members, we detected a multifold higher frequency of two pathogenic variants in the *SLC22A12* gene that are extremely rare in general population.

We found significantly increased expression of the five miRNAs in the plasma of patients with hyperuricemia, gout, or in patients during gout attack compared with a normouricemic control group. However, none of the observed miRNAs differed significantly between patient groups. Thus, we were unable to find a suitable biomarker of disease progression.

Genetic factors play a major role in the pathogenesis of primary hyperuricemia and gout as well as hereditary renal hypouricemia. Genetic analysis may predict the development of the disease in patients with a family history of gout. In patients with hypouricemia, genetic analysis may be essential in establishing the diagnosis of hereditary renal hypouricemia.

**Key words:** uric acid, urate transport, hypouricemia, hyperuricemia, gout