Abstract

There are localised proteins (so-called urate transporters) in the renal proximal tubules and in the intestine, which excrete and reabsorb uric acid. Polymorphisms in the genes coding these proteins can result in the disruption of the transport function and development of hyperuricemia and gout. However the serum level of uric acid is also determined by other factors which include the intake of exogenous purines in food, synthesis of endogenous purines and degradation of nucleic acids, but also certain conditions.

In 250 patients with primary hyperuricemia and gout we used Sanger sequencing to analyse the exons and adjacent intron regions in ten genes coding urate transporters: *ABCG2*, *ABCC4*, *SLC2A9*, *SLC22A12*, *SLC22A11*, *SLC22A13*, *SLC17A1*, *SLC17A3*, *SLC22A6* and *SLC22A8*. We examined a possible connection between the identified genetic variants and primary hyperuricemia and gout based on a comparison of allele frequencies with the European population, according to topological models, according to programs predicting the functional impacts of variants and searches in specialised literature. We also took into account the conclusions of functional studies analysing the impact of nonsynonymous variants in the *ABCG2* and *SLC2A9* genes. We also focused on the effect of the concomitant occurrence of several variants associated with hyperuricemia and gout, also on the combination of variants associated with hyperuricemia and gout with variants reducing the risk of gout.

In ten examined genes we identified ten polymorphisms most likely associated with primary hyperuricemia and gout found in the *ABCG2*, *SLC2A9* and *SLC22A8* genes. In the *SLC2A9* gene this was the p.L189L synonymous variant, for which the mechanism of the impact on the function of the protein is still unclear. In the *ABCG2* gene the frequent p.Q141K nonsynonymous variant, frequent c.1492+49G>T intron variant and the rare p.R147W, p.T153M, p.F373C, p.T434M, p.S467P and p.S572R nonsynonymous variants are associated with hyperuricemia. In the *SLC22A8* gene we identified the p.R149C variant, which could be associated with hyperuricemia. We also identified five polymorphisms, which most likely reduce the risk of gout. This was the p.V282I variant in the *SLC2A9* gene and the p.V12M, c.203+36A>G, c.1195-60A>T and c.1738-46G>A variants in the *ABCG2* gene.

In patients with the concomitant occurrence of polymorphisms associated with the level of uric acid and gout we found that the effect of the polymorphisms associated with gout prevails in a combination of variants increasing and decreasing the risk of gout. Marked hyperuricemia and an advanced stage of gout was observed in patients with some polymorphism associated with hyperuricemia and gout in combination with the frequent p.Q141K variant, which according to specialised studies is connected with the insufficient response to treatment with the uricostatic drug allopurinol.