Abstract

Uric acid excretion disorders are the most common cause of primary dysuricemia. The kidneys eliminate two-thirds of uric acid production and the other third is eliminated in the gastrointestinal tract. Renal reabsorption and secretion occur through the polarised epithelial cells in the proximal tubules. Uric acid transporters are expressed on these cell membranes. Reabsorption deficiency leads to hypouricemia and elevated fraction excretion associated with urolithiasis, nephrolithiasis or acute renal injury. Decreased uric acid secretion in the kidneys and small intestine leads to hyperuricemia, which develops into gout in 10% of individuals. Genome wide association studies detected a strong effect of *SLC22A12* (URAT1), *SLC2A9* (GLUT9) reabsorbing transporters and *ABCG2* (ABCG2) secreting transporter on uric acid serum concentration variability.

This thesis aimed to map out urate transporter allelic variants in a cohort of primary dysuricemia patients and identification of the variants causing defective uric acid excretion.

Six non-synonymous variants were described in *SLC22A12* (URAT1) and *SLC2A9* (GLUT9) genes in hypouricemic individuals, which had not been identified previously in any population studies. Significant decreases in uric acid transport have been demonstrated experimentally *in vitro,* expression of these variants cause defects in URAT1 or GLUT9 and reduces kidney reabsorption rates.

SLC22A12 (URAT1) a *SLC2A9* (GLUT9) allelic variants have been analysed in a cohort of 100 individuals with primary hyperuricemia and gout. Variant impact on protein localization in the cell or transport function was not confirmed experimentally in any cases identified in the cohort. Association between URAT1 and GLUT9 identified variants and hyperuricemia phenotype has not been established.

Nine unique non-synonymous variants were described in *ABCG2* (ABCG2) gene in a cohort of 250 patients with primary hyperuricemia and gout. The effect on expression levels or decreasing transport activity of ABCG2 was confirmed experimentally in six variants. Decreasing secretion *via* the kidneys or the intestine through ABCG2 causes primary hyperuricemia in individuals with these variants. Causality was not demonstrated in three of the variants studied. Further explanation for the lack of kidney excretion could be provided by investigation of NPT1 and NPT4 transporters on the apical membrane, and OAT1, OAT2, OAT3 transporters on the basolateral membrane of the proximal tubule epithelia due to its role in uric acid secretion.