Gender-dependent associations of uric acid levels with a polymorphism in SLC2A9 in Han Chinese patients

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Hyperuricaemia predisposes to gout and is associated with increased risk of cardiovascular disease probably through a relationship with other cardiovascular risk factors, including metabolic syndrome, hypertension, and renal disease (1), and possibly through an independent effect (2). Several new loci have been identified to be associated with serum uric acid levels and gout in recent genome-wide association studies (GWAS), with the strongest signals detected for the solute carrier family 2, member 9 gene (SLC2A9) variants in various populations (3–5). The present study examined associations of eight single nucleotide polymorphisms (SNPs) in five of the most relevant candidate genes with uric acid levels in Chinese patients with increased cardiovascular risk requiring statin therapy.

This study was conducted in Hong Kong Han Chinese patients with increased risk of coronary heart disease (CHD) (established CHD, familial hypercholesterolaemia, Table 1. Associations of genetic polymorphisms and uric acid levels.

| Polymorphisms          | n  | Males                  | Uric acid levels (mmol/L), mean ± SD | Females             | p  | n  | p  |
|------------------------|----|------------------------|--------------------------------------|---------------------|----|----|----|
| ABGG2 421C>A, rs2231142|    |                        |                                      |                     |    |    |    |
| CC                     | 91 | 0.383 ± 0.081          | > 0.05                               | 81                  | 0.322 ± 0.095       | > 0.05|
| CA                     | 56 | 0.376 ± 0.064          | > 0.05                               | 73                  | 0.329 ± 0.096       | > 0.05|
| AA                     | 17 | 0.381 ± 0.087          | < 0.05                               | 31                  | 0.317 ± 0.096       | > 0.05|
| ABGG2 34G>A, rs2231137 |    |                        |                                      |                     |    |    |    |
| GG                     | 63 | 0.388 ± 0.073          | > 0.05                               | 97                  | 0.319 ± 0.099       | > 0.05|
| GA                     | 77 | 0.386 ± 0.075          | > 0.05                               | 71                  | 0.333 ± 0.093       | > 0.05|
| AA                     | 21 | 0.382 ± 0.096          | > 0.05                               | 14                  | 0.301 ± 0.078       | > 0.05|
| CCL2-3813C>T, rs1860188|    |                        |                                      |                     |    |    |    |
| CC                     | 111| 0.386 ± 0.073          | > 0.05                               | 114                 | 0.326 ± 0.099       | > 0.05|
| CT                     | 46 | 0.385 ± 0.082          | > 0.05                               | 62                  | 0.322 ± 0.090       | > 0.05|
| TT                     | 7  | 0.416 ± 0.119          | > 0.05                               | 7                   | 0.323 ± 0.087       | > 0.05|
| GCKR rs1260326          |    |                        |                                      |                     |    |    |    |
| CC                     | 50 | 0.371 ± 0.076          | > 0.05                               | 52                  | 0.326 ± 0.108       | > 0.05|
| CT                     | 72 | 0.391 ± 0.074          | > 0.05                               | 84                  | 0.320 ± 0.090       | > 0.05|
| TT                     | 42 | 0.397 ± 0.079          | > 0.05                               | 42                  | 0.322 ± 0.095       | > 0.05|
| SLC2A9 rs1014290        |    |                        |                                      |                     |    |    |    |
| TT                     | 74 | 0.392 ± 0.069          | > 0.05                               | 70                  | 0.361 ± 0.093       | > 0.05|
| TC                     | 68 | 0.384 ± 0.079          | > 0.05                               | 83                  | 0.313 ± 0.087       | 8.6 × 10−6 |
| CC                     | 20 | 0.376 ± 0.097          | > 0.05                               | 31                  | 0.273 ± 0.090       | > 0.05|
| SLC2A9 rs12510549       |    |                        |                                      |                     |    |    |    |
| TT                     | 117| 0.387 ± 0.079          | > 0.05                               | 126                 | 0.318 ± 0.095       | > 0.05|
| TC                     | 42 | 0.383 ± 0.072          | > 0.05                               | 55                  | 0.332 ± 0.096       | > 0.05|
| CC                     | 5  | 0.412 ± 0.058          | > 0.05                               | 4                   | 0.390 ± 0.055       | > 0.05|
| SLC2A2 rs893006         |    |                        |                                      |                     |    |    |    |
| GG                     | 87 | 0.377 ± 0.067          | > 0.05                               | 116                 | 0.323 ± 0.089       | > 0.05|
| GT                     | 66 | 0.400 ± 0.088          | > 0.05                               | 54                  | 0.322 ± 0.102       | > 0.05|
| TT                     | 10 | 0.380 ± 0.059          | > 0.05                               | 10                  | 0.323 ± 0.102       | > 0.05|
| SLC2A2 rs1231825        |    |                        |                                      |                     |    |    |    |
| CC                     | 85 | 0.378 ± 0.068          | > 0.05                               | 117                 | 0.322 ± 0.089       | > 0.05|
| CT                     | 69 | 0.399 ± 0.088          | > 0.05                               | 58                  | 0.327 ± 0.107       | > 0.05|
| TT                     | 8  | 0.382 ± 0.052          | > 0.05                               | 10                  | 0.323 ± 0.102       | > 0.05|

ABGG2, ATP-binding cassette, subfamily G, member 2; CCL2, chemokine (C–C motif) ligand 2; GCKR, glucokinase regulatory protein; SLC2A9, solute carrier family 2, member 9; SLC2A2, solute carrier family 22, member 12.
The balance between urate reabsorption and secretion in the proximal renal tubules influences uric acid elimination and circulating uric acid concentrations. This study examined the associations between several renal transporter polymorphisms and plasma uric acid in Chinese patients with increased CHD risk receiving statin therapy. We found that the intronic SNP rs1014290 in SLC2A9 was significantly associated with reduced uric acid levels, which is consistent with previous GWAS findings showing that the strongest effect on serum uric acid concentrations was detected for several linked non-coding genetic variants of SLC2A9, including the rs1014290 polymorphism (3–5).

The SLC2A9 rs1014290 polymorphism had a more predominant effect on uric acid levels in females than males in the present study and in the GWAS in a range of genetic backgrounds including Caucasians, Blacks, and subjects from Mauritius (3, 4, 9). Although the exact mechanism of this gender-specific effect of SLC2A9 on uric acid levels is unclear, it has been shown that the expression of the urate transporter SLC22A12 was higher in male mice than in female mice and testosterone was shown to increase the transcription and expression of SLC22A12 in cell lines, suggesting a role for sex hormones in regulating the expression of SLC2A9 and other urate transporters (10). We also found that the association between SLC2A9 rs1014290 and uric acid level was more significant in patients without hypertension than those with hypertension, and this may be due to the influence of the disease itself and/or the use of anti-hypertensive drugs in patients with hypertension.

This study has several limitations. First, the lack of association of uric acid levels with the other SNPs examined in the study may be due to the small sample size. Second, the study participants were treated with multiple pharmacotherapy for the CHD risk factors, in particular statins, which may influence uric acid levels and/or their associations with genetic polymorphisms. In conclusion, the common SLC2A9 rs1014290 polymorphism was significantly associated with reduced uric acid levels in Chinese female patients with increased CHD risk.

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Methotrexate therapy, rheumatoid arthritis, and life-threatening liver complications: should we be monitoring more closely?

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Methotrexate (MTX) is currently first-line therapy for rheumatoid arthritis (RA). MTX can cause elevated liver enzymes, which occurs in 20% of patients, but only 3.7% cease MTX completely (1). Prolonged therapy and age are risk factors for development of hepatic disease as well as alcohol, diabetes, obesity, and prior hepatitis infection (2). American College of Rheumatology (ACR) guidelines quote an incidence of MTX-induced cirrhosis of 1/1000 after 5 years of treatment (3). Toxicity is usually manifest by persistent elevation of transaminases [alanine aminotransferase (ALT) and aspartate aminotransferase (AST)] and guidelines suggest clinicians withdraw or reduce MTX dose and consider liver biopsy. Alkaline phosphatase (ALP) measurement is non-compulsory but ALT/AST levels are essential criteria for safe surveillance, a view recently endorsed by a multinational review panel (4). In this letter we describe the case of a patient with RA who developed life-threatening complications from liver disease, after low-dose MTX, in the presence of normal transaminases.

A 26-year-old Caucasian woman with seropositive RA presented acutely unwell with abdominal pain and massive haematemesis. She had had RA for 4 years and had taken MTX 20 mg weekly, hydroxychloroquine (HCQ) 400 mg daily, and folic acid (FA) 5 mg weekly since diagnosis. She had received two doses of golimumab 50 mg, a novel anti-tumour necrosis factor (anti-TNF) therapy, but there was no exposure to other medications. Assessment demonstrated hypovolaemic shock, abdominal tenderness, anaemia, and evidence of synthetic liver dysfunction. Emergency gastroscopy revealed bleeding oesophageal varices, which were ligated. Ultrasound scan (USS) showed parenchymal liver disease, ascites, portal hypertension (without evidence of hepatic or portal vein thromboses) and a normal biliary system. MTX was halted and folic acid (FA) 5 mg weekly, hydroxychloroquine (HCQ) 400 mg daily, and avoidance of hepatotoxic disease-modifying anti-rheumatic drugs (DMARDs), with a view to commencing etanercept.

Despite receiving less than 4 g of MTX, this patient developed cirrhosis and portal hypertension, which...