Genomic Influences on Hyperuricemia and Gout

Tony Merriman, PhD

KEYWORDS

• Genome-wide association studies • Gout • Hyperuricemia • ABCG2 • SLC2A9 • Urate • Uric acid

KEY POINTS

- Genome-wide association studies have identified nearly 30 loci associated with urate concentrations, dominated by loci containing renal and gut uric acid excretion regulators.
- The SLC2A9 gene, that encodes a renal uric acid reuptake transporter, has a major effect on urate concentrations and the risk of gout, and exhibits non-additive interactions with sex and dietary exposures.
- The ABCG2 gene, that encodes a gut and renal uric acid secretory transporter, also has a major effect. The causal 141K variant results in ABCG2 internalization with the defect able to be rescued by small molecules.
- To date only small genome-wide association studies have been done in gout meaning that little is known about the genetic control of progression from hyperuricemia to gout.

INTRODUCTION

Gout is an inflammatory arthritis caused by an extremely painful but self-limiting innate immune response to monosodium urate (MSU) crystals deposited in synovial fluid.[1] Without effective management, in some individuals, gout can become chronic, with the development of tophi (organized lumps of urate and immune cells[2]) and permanent bony erosion and disability. Gout is also comorbid with other metabolic-based conditions, such as heart and kidney disease and type 2 diabetes,[3] with the causal relationships that are of much clinical interest, remaining unclear. An elevated concentration of serum urate (hyperuricemia) is necessary, but not sufficient, for the development of gout with host-specific and environmental factors required for the progression from hyperuricemia to gout. Approximately 30 genetic loci, including *SLC2A9* and *ABCG2* that have major effects, influence serum urate concentrations[4] with less understood about the genetic control of the formation of MSU crystals and the subsequent inflammatory response. Urate-lowering therapy, in particular use of the

Department of Biochemistry, University of Otago, 710 Cumberland Street, Dunedin 9054, New Zealand
E-mail address: tony.merriman@otago.ac.nz

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xanthine oxidase inhibitor allopurinol, is a cornerstone of gout management, but for a variety of reasons it is often not effective.[1]

Hyperuricemia and gout are more prevalent in men than women, with the prevalence of both increasing with age and particularly in women after menopause.[5] The prevalence of gout is typically 3% to 4% in people of European ancestry, up to 1% in populations of Asian ancestry, and 6% to 8% in Taiwanese Aboriginals and Polynesian people (Maori and Pacific Islanders) living in New Zealand.[5] The increased prevalence of gout in the latter populations has a strong contribution from the inherent hyperuricemia in these groups.[6,7] Serum urate levels are a balance of overproduction and renal and gut underexcretion,[8] with renal excretion particularly important. The renal fractional excretion of uric acid is reduced in hyperuricemia compared with normouricemia, in men compared with women, and in Pacific Islanders and New Zealand Maori compared with Europeans.[9,10] Regarding overproduction, urate is the end product of purine metabolism, with the liver a major site of production. For example, the liver produces urate as a by-product of fructose and alcohol-induced purine nucleotide degradation.

Monogenic disorders of purine metabolism including hypoxanthine-guanine phosphoribosyltransferase deficiency (Lesch-Nyhan syndrome) and 5-phosporibosyl-1-pyrophosphate synthetase superactivity generate rare pediatric syndromes of hyperuricemia, early-onset gout, and kidney stones. Familial juvenile hyperuricemic nephropathy is a disorder of renal uric acid underexcretion caused by mutations in uromodulin leading to hyperuricemia, early-onset gout, and chronic kidney disease. These rare disorders provide insights into purine metabolism and renal uric acid excretion mechanisms but account for an extremely small proportion of hyperuricemia and gout in the general population. Genome-wide association studies (GWAS) for common genetic variants contributing to the polygenic component of hyperuricemia and gout in the general population exhibit very little to no overlap (with the possible exception of a locus containing the *PRPSAP1* gene) with monogenic disorders. This review, therefore, focuses on insights into the common genetic variants contributing to the development of gout, in particular on recent and other pertinent findings regarding the 2 major urate and gout loci, *SLC2A9* and *ABCG2*.

GENOME-WIDE ASSOCIATION STUDIES IN URATE

In the context of medically important metabolites, urate is very tractable to research on etiology. It is easily measured and levels typically do not fluctuate over short periods; this allows good quality of phenotyping for studies of genetic and environmental risk factors. Approximately 90% of variance in renal uric acid handling and approximately 60% of variance in serum urate concentrations are explained by inherited genetic variants.[11,12] The largest GWAS to date was carried out in people of European ancestry.[4] A total of 110,347 individuals were genotyped at 2.45 million single nucleotide polymorphism (SNP) markers. Of these markers, 2201 were associated with serum urate concentrations at an experiment-wide level of significance ($P<5 \times 10^{-8}$) that accounts for the multiple testing inherent in a GWAS. These markers were spread over 28 distinct regions of the genome; each region can be considered a locus containing one or more genetic variants with a causal role in determining serum urate concentrations. Predictably, most of these loci are also associated with the risk of gout in multiple ancestral groups.[4,13,14] Within the 28 loci, renal and gut uric acid excretion genes are prominent, some with a very strong effect, particularly *SLC2A9* and *ABCG2*. The urate-raising allele at *SLC2A9* associates with an average 0.37 mg/dL increase in serum urate, the urate-raising allele at *ABCG2* with an average 0.22 mg/dL increase.