The Genetic Basis of Gout

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KEYWORDS

• Gout • Urate • Gene • Association • Genome-wide association studies • *SLC2A9* • *ABCG2*

KEY POINTS

- Genome-wide association studies for serum urate have identified 28 loci influencing serum urate levels.
- The largest genetic effects on serum urate are within genes encoding transporters that excrete uric acid in the kidney and gut.
- Other genetic effects are within glycolysis genes.
- There are interactions between genes, and environmental influences on serum urate (diuretics, alcohol, sugar-sweetened beverages).
- Genome-wide association studies are required in gout using well-phenotyped cases to identify loci controlling progression from hyperuricemia to inflammatory gout.

INTRODUCTION

The central feature of gout is deposition of inflammatory monosodium urate (MSU) monohydrate microcrystals, which can lead to acute inflammatory arthritis, tendonitis, cartilage damage, and bone remodeling. Several checkpoints exist in the pathogenesis of gout (reviewed in Refs.[1,2]). Central to the development of gout is elevated tissue concentrations of urate, which in some individuals lead to formation of MSU crystals. Elevated serum urate levels (hyperuricemia) occur as a result of increased production of hepatic urate through the purine synthesis de novo and salvage pathways; however, renal underexcretion of uric acid is a dominant contributor, with reduced fractional excretion of uric acid in hyperuricemia and gout.[3–5] Once formed, MSU crystals may induce an acute inflammatory response leading to acute gouty arthritis and/or a chronic granulomatous response with formation of tophi. Although hyperuricemia is present in virtually all people with gout, this biochemical abnormality is not sufficient for the development of clinically apparent joint disease, as most people with hyperuricemia do not develop gout.[6]

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Monogenic inborn errors of purine metabolism such as hypoxanthine-guanine phosphoribosyltransferase deficiency (Lesch-Nyhan syndrome) and 5-phosphoribosyl-1-pyrophosphate synthetase superactivity lead to rare pediatric syndromes of hyperuricemia, associated with neurodevelopmental disorders, early-onset gout, and kidney stones. In addition, familial juvenile hyperuricemic nephropathy is an autosomal dominant disorder of renal uric acid underexcretion caused by mutations in the uromodulin gene that leads to severe underexcretion-type hyperuricemia, early-onset gout, and chronic kidney disease. These rare monogenic disorders provide important insights into physiologic purine metabolism and uric acid excretion mechanisms, but do not account for the vast majority of hyperuricemia or gout observed in the general population. Renal uric handling of acid and hyperuricemia have a large heritable component (87% for fractional excretion of uric acid,[7] 60% for serum urate).[8] Consistent with these observations, genome-wide association studies (GWAS) have revealed that a polygenic component of common inherited variants[9] contributes to the development of gout in the general population with, excepting the PRPSAP1 locus, little overlap with monogenic syndromes. This review focuses on recent insights into these common genetic variants that contribute to the development of gout, and their potential interaction with environmental risk factors.

GENOME-WIDE ASSOCIATION STUDY FINDINGS FOR SERUM URATE

Over the past 8 years, GWAS and subsequent meta-analyses have led to a considerable expansion in the knowledge of common genetic loci that are associated with hyperuricemia and gout in Europeans. Two meta-analyses, each involving more than 28,000 participants, found genome-wide genetic loci that are reproducibly associated with serum urate levels or gout (**Table 1**).[10,11] In 2009, a meta-analysis by Kolz and colleagues[10] reported associations between 9 common genetic variant loci and serum urate concentrations: *SLC2A9*, *ABCG2*, *SLC22A12*, *SLC17A1*, *SLC22A11*, *SLC16A9*, *GCKR*, *LRRC16A*, and near *PDZK1*. In 2010, a meta-analysis of the CHARGE consortium by Yang and colleagues[11] reconfirmed 6 of these loci (*SLC2A9*, *ABCG2*, *SLC17A1*, *SLC22A11*, *GCKR*, and *PDZK1*) and additionally identified the *R3HDM2-INHBC* region and *RREB1* loci with genome-wide significance. The genetic urate risk score was strongly associated with the risk of gout. An Icelandic GWAS for serum urate, using whole genome sequence data in 15,506 individuals, identified 4 loci with a genome-wide level of significance[12] at *SLC2A9*, *ABCG2*, *PDZK1*, and *ALDH16A1*. The variant underlying the *ALDH16A1* association appears to be a previously unreported Icelandic-specific genetic variation present at a frequency of 1.8%, which encodes a proline to arginine amino acid change in the ALDH16A1 protein. It was estimated that the variant explained 0.5% of variance in serum urate in the Icelandic population.[12]

In other ancestral groups, a meta-analysis[13] and a GWAS[14] have demonstrated that 10 of the 11 loci that have been shown to influence serum urate levels in individuals with European ancestry were also significantly associated with serum urate or gout in African American sample sets. The GWAS in African Americans also identified a novel locus influencing serum urate near the *SLC2A12* gene on chromosome 6.[13] This gene is a good candidate, as it is a glucose transporter and a member of the same family as *SLC2A9*, which has a very strong influence on serum urate across populations.[9,13,15] Another GWAS among East Asians by Okada and colleagues[15] in 2012 showed genome-wide significance of serum urate levels with *SLC2A9*, *ABCG2*, *SLC22A12*, and *MAF*; all of these loci overlap with those identified in Europeans (see below). A previous study in Japanese had identified *SLC2A9*, *ABCG2*,