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THE GENETICS OF HYPERURICEMIA AND GOUTY NEPHROPATHY

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Abstract
Gout is a common joint disease caused by hyperuricemia. This article provides new information on the genes that cause gouty nephropathy, including the results of genomic studies. Most gout-related genes are involved in the renal urate transport system. For example, the urate carrier genes SLC2A9, ABCG2, and SLC22A12 modulate uric acid levels and hence the risk of developing gout. SLC2A9 and SLC22A12 genes provide the balance of uric acid absorption and secretion in the kidneys. It is here that mutations in these genes upset this balance.The discovery of these genes greatly expands our understanding of the role of urate carriers in the pathogenesis of gout.

Keywords: gout, gouty nephropathy, gene, GWAS.

Gout is a common and very painful inflammatory arthritis caused by hyperuricemia. This review provides an update on the genetics of hyperuricemia and gout, including the results of whole-genome association studies. Most genes associated with serum uric acid levels or gout are involved in the renal urate transport system. For example, the urate transporter genes SLC2A9, ABCG2, and SLC22A12 modulate serum uric acid levels and gout risk. The net balance between renal absorption and urate secretion is a major determinant of serum uric acid concentration and loss-of-function mutations in SLC2A9 and SLC22A12.cause inherited hypouricaemia due to reduced urate absorption and unimpeded urate secretion. However, the differences in serum uric acid levels attributable to genetic variants are small, and their clinical utility in predicting gout risk seems limited because serum uric acid levels effectively predict gout risk. Urate-associated genes and genetically determined serum uric acid levels

are not significantly associated with cardiovascular metabolic outcomes, calling into question the hypothesis of a causal role of serum uric acid in the development of cardiovascular disease. Strong pharmacogenetic associations between HLA-B*5801 alleles and severe allopurinol hypersensitivity reactions have been shown in Asian and European populations. Genetic testing for HLA-B*5801 alleles may be used to predict these potentially lethal side effects.

Gout, the most common inflammatory arthritis, is caused by hyperuricemia and results in significant morbidity associated with excruciating pain. 1 , 2 The disease affects about 8.3 million people in the United States 1 and is a significant socioeconomic burden. 3 Gout is closely associated with metabolic syndrome, 4 myocardial infarction, diabetes, and premature death.

Thomas Sydenham recognized the familial nature of hyperuricemia and gout in 17. However, until the last decade, knowledge about the role of specific genes in the pathogenesis of gout was limited to those associated with rare monogenic metabolic and renal disorders. Mutations in genes that encode enzymes involved in purine synthesis and interconversion lead to uric acid hyperproduction and are associated with familial disorders such as glycogen accumulation diseases characterized by excessive cell death and ATP degradation. In contrast, mutations leading to decreased urate excretion are associated with inherited renal diseases such as medullary cystic kidney disease 1 and 2 are often associated with additional clinical features unrelated to gout.

Refuting the early claim that familial gout can be caused by monogenic influences, twin and family studies have shown a polygenic type of inheritance of both hyperuricemia and fractional urate excretion (FEua) by the kidneys. In one twin study, the inheritance of renal urate clearance was ~60%, whereas the estimated inheritance of FEua was ~87%. Other studies have shown that serum urate levels have a significant heritable component (~40%). The overall pattern of inheritance is best explained by a complex model involving interactions between more than one major gene, several modifying genes, and environmental factors. This conclusion is supported by the Framingham Heart Study, population-based studies of Pacific Islanders, and whole-genome association studies (GWAS), which have identified several novel genetic variants associated with serum uric acid levels.

Over the past 7 years, GWAS, repeat studies, and meta-analyses have led to a significant increase in our knowledge of common genetic variants that predispose to hyperuricemia and gout. The discovery of these new genes has significantly expanded our understanding of the role of renal urate transporters in the pathogenesis of these diseases. In this review, we describe the associations between common genetic

variants, serum uric acid levels, and gout, and the role of these variants in the pathogenesis of hyperuricemia and gout. We also briefly discuss the association between gout, cardiovascular disease, and metabolic syndrome, as well as the pharmacogenetic link between HLA-B*5801 and severe hypersensitivity reactions to allopurinol.

Genetic associations

Most of the novel genes associated with hyperuricemia or gout in GWAS encode proteins involved in the renal urate transport system. This finding is not surprising, as reduced renal urate excretion is responsible for up to 90% of cases. A group of related urate transporters that are expressed at the apical border of the renal proximal tubules have been termed "uric acid transporters" because of their interactive nature in the regulation of urate homeostasis. Transport components include glucose transporter type 9 (GLUT-9, also known as SLC2A9); urate anion transporter 1 (URAT1, also known as SLC22A12); organic anion transporters, solute carrier family 22, member 6, member 8, member 11 and member 13 (SLC22A6, SLC22A8, SLC22A11 and SLC22A13, also known as OAT1, OAT3, OAT4 and ORCTL-3); Multidrug resistance-related protein 4 (MRP4); sodium-related monocarboxylate transporter 1 and 2 (SLC5A8 and SLC5A12); and member 2 of ATP-binding cassette subfamily G (ABCG2, also known as breast cancer resistance protein). Almost all apical absorptive and secretory transporters terminate with recognition motifs for binding to PDZ domain proteins such as PDZK1. These framework proteins bind transporters in the apical complex. Notably, PDZK1 is also a genetic determinant of serum uric acid levels.

SLC2A9

GLUT-9 is encoded by the SLC2A9 gene . Several GWAS have identified genetic variants of SLC2A9 , which have been strongly associated with serum uric acid levels. In these studies, SLC2A9 variation was the most statistically significant genetic determinant of serum urate; representing 3.4-8.8% variance in women and 0.5-2.0% variance in men. Loss-of-function mutations in the SLC2A9 gene cause renal hypouricemia and SLC2A9 variants have been associated with determinations of gout in whites, Chinese and Polynesians , and with low FEua in cohorts in Germany, the UK and Croatia. These findings are consistent with the critical role of GLUT-9 in reabsorption of filtered urate by proximal tubules.

Studies using Xenopus oocytes have shown that GLUT-9 is a reliable urate transporter that can be partially inhibited by uricosuric agents such as probenecid, losartan, benzbromaron and tranilast as well as the glucose transporter inhibitor floretin. It has been reported that this protein is a fructose transporter and possibly a fructose and

urate exchanger, but some studies have not confirmed fructose as a substrate. GLUT-9 does not undergo cis -inhibition or trans -stimulation in response to pyrazinoate and related anions, so it does not appear to act as a urate-anion exchanger (DB Mount, unpublished data). Moreover, GLUT-9 is activated by membrane depolarization and therefore may function as a urate uniporter or electrogenic exchanger.

Two different N-terminal isoforms of human GLUT-9 were identified: GLUT-9a (540 residues) and GLUT-9b (511 residues, also known as GLUT9ΔN). These isoforms are generated by alternative splicing of the 5'-termini and differ in membrane transport. In Madin-Darby dog kidney cells that have been transfected with human GLUT-9, GLUT-9a is transferred to the basolateral membrane and GLUT-9b is transferred to the apical membrane. Leukocyte expression of GLUT-9b mRNA is more closely correlated with serum uric acid levels than GLUT-9a mRNA expression. This finding suggests that GLUT-9b plays a more essential role in urate homeostasis than GLUT-9a. Protein and mRNA of both isoforms have been detected in human kidneys, but detailed localization studies have not yet been performed. However, expression at the basolateral membrane suggests that GLUT-9a probably functions as an exit site for urate from proximal tubule cells, whereas GLUT-9b may transport urate to proximal tubule cells through the apical membrane.

GLUT-9 is expressed in hepatocytes (both isoforms), chondrocytes (GLUT-9a), intestinal cells (GLUT-9a) and leukocytes (both isoforms), and renal epithelial cells (both isoforms). GLUT-9 expression in articular cartilage chondrocytes suggests a possible role for SLC2A9 variants in the development of sodium urate crystal-induced arthritis. Further understanding of the regulation of urate transporters at the tissue level may provide insight into the mechanisms of tophus formation and possibly crystal-induced joint inflammation.

The causative variant or variants within SLC2A9 for determining serum uric acid concentration have not yet been identified. However, progress has been made in the accurate mapping of the GWAS signal. Significant coding sequence variation exists in SLC2A9, and at least 24 annotated non-synonymous variants have been identified. With the exception of loss-of-function mutations associated with familial hypouricemia, no systematic characterization of the transport phenotypes of variants encoding SLC2A9 has been performed . The overall contribution of coding sequence variation in SLC2A9Urath homeostasis is unclear because of population heterogeneity and linkage disequilibrium (non-random association of alleles at two or more loci) within a gene. For example, the biochemically conserved Val253Ile variant is closely associated with serum uric acid levels in some but not all studies. However, the presence of both the Val253Ile allele and the common allele in the protective and

susceptible haplotype in Pacific Islanders suggests that the Val253Ile variant does not play a significant role in susceptibility to gout in this population. Similarly, the Arg265His variant has been associated with hyperuricemia and severe gout in some but not all populations.

ABCG2

Associations between ABCG2 polymorphisms and uric acid levels have been consistently demonstrated in GWAS and replicated in gout cases in several populations. ABCG2 is expressed in the brush cage membrane of renal proximal tubules and plays a role in apical urate secretion. The transporter is also abundantly expressed in the apical membrane of epithelial cells in the small intestine and in the liver, suggesting a possible role in extrarenal uric acid excretion. Interestingly, ABCG2 mRNA levels are increased by statins in the human hepatoma cell line, HepG2. Functional studies of the mechanism of this activation may provide data that could potentially lead to the development of improved treatments for gout.

In white, African and Asian populations, the strongest association between ABCG2 and gout is associated with the rs2231142 single nucleotide polymorphism (SNP) in exon 5, which causes an amino acid substitution of Glu141Lys. Meta-analysis of GWAS data showed that the Glu141Lys polymorphism accounts for 0.57% of the variation in serum urate. Interestingly, the polymorphism had a greater effect on serum uric acid levels in men than in women. Functional studies of the Glu141Lys substitution showed that it causes a 53% reduction in ABCG2-mediated urate transport rate compared with wild-type ABCG2. The associated decrease in urate secretion may lead to an imbalance between net secretion and absorption, promoting absorption and thus leading to hyperuricemia.

Analysis of a community-based atherosclerosis risk study showed that at least 10% of all gout cases in white people were associated with the Gln141Lys causal variant. However, the frequency of the Gln141Lys risk allele has been reported to be as high as 32% in Asian populations. Although both Maori and Pacific Islanders are known to have an increased risk of gout, the Gln141Lys variant is strongly associated with gout only in West Polynesians. This distribution may be the result of random depletion of the allele during the eastward migration, as the frequency of the Gln141Lys variant in white populations is <12%.

Conclusions

GWAS have led to a significant increase in reproducible data on the genetic association of serum uric acid and gout. Reduced renal urate excretion is a major cause

of hyperuricemia and gout, and most of the common genes found in GWAS are involved in the renal urate transport system. The urate transporter genes, GLUT-9 and ABCG2, which are important modulators of uric acid levels, are consistently associated with serum uric acid levels and gout. Although GWAS association data for SLC22A12 (which encodes URAT1) have been less impressive, many layers of evidence indicate that URAT1 is an important component of urate transport in the kidneys. Loss-of-function mutations in the SLC22A12 or SLC2A9absorption transporter genes result in dominant urate secretion and hypouricemia, whereas loss-of-function mutations in the secretory urate transporter genes, ABCG2, SLC17A1 or SLC17A3, cause hyperuricemia. These data show that serum uric acid levels are largely determined by the relative balance between urate absorption and secretion in the proximal tubules. Most of the other replicated genetic variants discussed in this review require further functional characterization. However, these genetic data add significantly to our understanding of the pathogenesis of hyperuricemia and gout. Future research directions may include replication in other ethnic cohorts, accurate mapping and repeat sequencing, functional studies of identified genetic variants, and evaluation of potential interactions between genes and key environmental factors. Genetic markers associated with severe gout (such as erosive gout), other complications of gout, or the efficacy and adverse reactions of antipodagger drugs should also be evaluated.

Key Points

■ Most genes associated with hyperuricemia and gout have been implicated in the renal urate transport system in whole-genome association studies.

■ Genetic variability explains only a small level of variability in serum uric acid levels (~6%).

Serum uric acid levels are determined by the net balance between urate absorption and secretion, which is mediated by separate sets of transporters in the proximal renal tubules.

■ The clinical value of testing for urate-related genes seems limited because serum urate levels alone can effectively predict gout risk at low cost.

■ Urate-associated genes and genetically determined urate levels are not significantly associated with cardiovascular or metabolic outcomes, suggesting that serum uric acid does not play a causal role in these outcomes.

■ Strong pharmacogenetic associations between HLA-B*5801 alleles and severe allopurinol hypersensitivity reactions have been shown in Asian and European populations, demonstrating the clinical utility of testing these alleles.

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