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The genetics of hyperuricaemia and gout

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Abstract

Gout is a common and very painful inflammatory arthritis caused by hyperuricaemia. This Review provides an update on the genetics of hyperuricaemia and gout, including findings from genome-wide association studies. Most of the genes that 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 urate absorption and secretion is a major determinant of serum uric acid concentration and loss-of-function mutations in *SLC2A9* and *SLC22A12* cause hereditary hypouricaemia due to reduced urate absorption and unopposed urate secretion. However, the variance in serum uric acid explained by genetic variants is small and their clinical utility for gout risk prediction seems limited because serum uric acid levels effectively predict gout risk. Urate-associated genes and genetically determined serum uric acid levels were largely unassociated with cardiovascular–metabolic outcomes, challenging 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 were shown in Asian and European populations. Genetic testing for *HLA-B*5801* alleles could be used to predict these potentially fatal adverse effects.

Introduction

Gout, the most common inflammatory arthritis, is caused by hyperuricaemia and leads to substantial morbidity associated with excruciating pain.[1,2] The disease affects ~8.3 million people in the USA[1] and is a substantial socioeconomic burden.[3] Gout is strongly associated with metabolic syndrome,[4] myocardial infarction,[5–7] diabetes[8] and premature death.[7]

Thomas Sydenham recognized the familial nature of hyperuricaemia and gout in the 17th century.[9] However, until the past decade, knowledge of the roles of specific genes in the pathogenesis of gout was limited to those that are associated with rare monogenic metabolic

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Competing interests
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and renal disorders (Table 1).[10–22] Mutations in genes that encode enzymes involved in purine syn thesis and interconversion lead to overproduction of uric acid and are associated with familial disorders such as glycogen storage diseases, which are charac terized by excessive cell death and ATP degradation.[12–14] By contrast, mutations that lead to reduced excretion of urate are associated with hereditary renal disorders, such as medul lary cystic kidney disease type 1 and 2.[18–20] Monogenic dis orders of purine pathways usually present in childhood or early adulthood and are often associated with additional non gouty clinical features.[23]

Disproving the early contention that familial gout might be due to monogenic influences, studies of twins and families have shown a polygenic mode of inheritance for both hyperuricaemia and the fractional excretion of urate (FEua) by the kidneys.[24] In one study of twins, the heritability of the renal clearance of urate was ~60%, whereas the estimated heritability of FEua was ~87%.[25] Other studies have shown that serum urate levels have a substantial heritable component (~40%).[26] The overall pattern of inheritance is best explained by a complex model incorporating interactions between more than one major gene, several modifying genes and environmental factors.[26] This conclusion is supported by findings from the Framingham Heart Study,[27] population studies of Pacific Islanders,[23] and genome-wide association studies (GWAS) that have identified multiple novel genetic variants that associate with serum uric acid levels.[23,28]

Over the past 7 years, GWAS, replication studies and meta-analyses have led to a remarkable increase in our knowledge of common genetic variants that predispose to hyperuricaemia and gout (Figure 1). The discovery of these novel genes has substantially increased our understanding of the role of renal urate transporters in the pathogenesis of these disorders. In this Review, we describe the associations between common genetic variants, serum uric acid levels and gout as well as the role of these variants in hyperuricaemia and gout patho genesis. We also briefly discuss the association between gout, cardiovascular disease and metabolic syndrome and the pharmacogenetic associations between *HLA-B*5801* and severe allopurinol-hypersensitivity reactions.

Genetic associations

The majority of the novel genes that have associated with hyperuricaemia or gout in GWAS encode proteins that are involved in the renal urate-transport system (Figure 2). This finding is unsurprising because reduced renal excretion of urate is the cause of the disorders in up to 90% of cases.[2] The group of related urate transporters that are expressed on the apical border of renal proximal tubules have been termed the ‘uric acid transportasome’ because of their interactive nature in regulating urate homeostasis (Figure 2).[29,30] Components of the transporta some include glucose transporter type 9 (GLUT-9 also known as SLC2A9);[31] urate anion transporter 1 (URAT1, also known as SLC22A12); the 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); multi-drug resistance-associated protein 4 (MRP4); sodium-coupled monocarboxylate transporter 1 and 2 (SLC5A8 and SLC5A12) and ATP-binding cassette subfamily G member 2 (ABCG2, also known as breast cancer resistance protein).[23] Almost all of the apical absorptive and secretory transporters end with recognition motifs for binding to PDZ domain proteins, such as PDZK1. These scaffolding proteins tether the transporters in an apical complex.[30] Notably, PDZK1 is also a genetic determinant of serum uric acid levels.[32,33]

SLC2A9

GLUT-9 is encoded by the *SLC2A9* gene. Several GWAS identified genetic variants of *SLC2A9* that were robustly associated with serum uric acid levels.[34–38] In these studies, variation in *SLC2A9* was the most statistically significant genetic determinant of serum urate; accounting for 3.4–8.8% of the variance in women and 0.5–2.0% of the variance in men.[34–39] Loss-of-function mutations in the *SLC2A9* gene cause renal hypouricaemia[40,41] and *SLC2A9* variants have been associated with case definitions of gout in white, Chinese and Polynesian populations,[26,34,37,39,42] as well as with low FEua in German, British and Croatian cohorts (Table 2).[31,34,35,43,44] These finding are consistent with the critical role of GLUT-9 in the reabsorption of filtered urate by proximal tubules.

Studies using *Xenopus* oocytes have shown that GLUT-9 is a robust urate transporter[34,31,40,41] that can be partially inhibited by uricosuric agents, such as probenecid, losartan, benzbromarone[31,32,41] and tranilast,[45] as well as by the glucose transporter inhibitor phloretin.[46] The protein was reported to be a fructose transporter,[47] and potentially a fructose–urate exchanger,[31,34] but some studies have not confirmed that fructose is a substrate.[41] GLUT-9 does not undergo *cis*-inhibition or *trans*-stimulation in response to pyrazinoate and related anions so does not seem to function as a urate–anion exchanger (D. B. Mount, unpublished data). More over, GLUT-9 is activated by membrane depolarization[41] and, therefore, might function as a urate uniporter or electrogenic exchanger.

Two distinct *N*-terminal isoforms of human GLUT-9 have been identified: GLUT-9a (540 residues) and GLUT-9b (511 residues, also known as GLUT9ΔN).[48] These isoforms are generated by alternative splicing of 5' ends and differ in membrane trafficking.[48] In Madin–Darby canine kidney cells that were transfected with human GLUT-9, GLUT-9a trafficked to the basolateral membrane and GLUT-9b to the apical membrane.[48] Leukocyte expression of GLUT-9b mRNA correlates more closely with serum uric acid levels than GLUT-9a mRNA expression.[35] This finding suggests that GLUT-9b has a more substantial role in urate homeostasis than GLUT-9a. Protein and mRNA from both isoforms have been detected in human kidney,[48] but detailed localization studies have not yet been carried out. However, expression at the basolateral membrane suggests that GLUT-9a is likely to function as the exit site for urate from proximal tubule cells, whereas GLUT-9b might transport urate into the proximal tubule cells across the apical membrane (Figure 2).

GLUT-9 is expressed in hepatocytes (both isoforms), chondrocytes (GLUT-9a),[34,49] intestinal cells (GLUT-9a) and leukocytes (both isoforms), as well as in renal epithelial cells (both isoforms).[48,50] Expression of GLUT-9 in articular cartilage chondrocytes suggests a possible role of *SLC2A9* variants in the development of mono-sodium urate crystal-induced arthritis.[34,49] Further understanding of the regulation of urate transporters at the tissue level might provide insight into the mechanisms of tophi formation, and perhaps crystal-induced joint inflammation.

The causal variant or variants within *SLC2A9* for determination of serum uric acid concentration have not yet been identified. However, progress has been made in fine-mapping the GWAS signal.[51] Considerable variation in coding sequence exists in *SLC2A9* and at least 24 annotated nonsynonymous variants have been identified.[52] With the exception of loss-of-function mutations associated with familial hypouricaemia,[40,41,53,54] there has been no systematic characterization of the transport phenotypes of *SLC2A9* coding variants. The overall contribution of coding sequence variation in *SLC2A9* to urate homeostasis is not clear because of population heterogeneity and linkage disequilibrium (nonrandom association of alleles at two or more loci) within the gene. For example, the biochemically conservative Val253Ile variant associated strongly with serum uric acid levels

in some,[37,55] but not all, studies.[34,38] However, the presence of both the Val253Ile allele and the common allele on the protective and susceptibility haplotypes in Pacific Islanders suggests that there is not a substantial role for the Val253Ile variant in gout susceptibility in this population.[42] Similarly, the Arg265His variant was associated with hyperuricaemia[56,57] and severe gout[57,58] in some, but not all, populations.[55]

ABCG2

Associations between *ABCG2* polymorphisms and uric acid levels have been consistently demonstrated in GWAS and replicated in gout cases from several populations (Table 2).[37,39,59–62] *ABCG2* encodes ABCG2, a multifunctional transporter that belongs to the ATP-binding cassette family and mediates the efflux of various compounds in an ATP-dependent manner.[63] ABCG2 is expressed in the brush border membrane of the proximal tubules of the kidney and has a role in the apical secretion of urate.[62] 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 the extrarenal excretion of uric acid.[64] Interestingly, *ABCG2* mRNA levels are upregulated by statins in the human hepatoma cell line, HepG2.[65] Functional studies of the mechanism of this upregulation might provide data that could potentially lead to the development of improved therapies for gout.

In white, African and Asian populations, the strongest association between *ABCG2* and gout involved the single nucleotide polymorphism (SNP) rs2231142 in exon 5,[37] which causes a Glu141Lys amino acid substitution. A meta-analysis of GWAS data showed that the Glu141Lys polymorphism accounted for 0.57% of the variation in serum urate.[32] Interestingly, the poly morphism had a larger effect on serum urate levels in men than in women.[32] Functional studies of the Glu141Lys substitution have shown that it causes a 53% reduction in the rate of ABCG2-mediated urate transport compared with wild-type ABCG2.[62] The associated reduction in urate secretion might lead to an imbalance between net secretion and absorption, favouring absorption and thus leading to hyperuricaemia.

An analysis of the Atherosclerosis Risk in Communities study showed that at least 10% of all gout cases in white individuals were attributable to the Gln141Lys causal variant.[62] However, the frequency of the Gln141Lys risk allele has been reported to be as high as 32% in the Asian population.[32,60] Although both Maoris and Pacific Islanders are known to have an increased risk of gout, the Gln141Lys variant is strongly associated with gout only in the western Polynesian population.[61] This distribution might be the result of chance depletion of the allele during eastward migration, as the frequency of the Gln141Lys variant in white populations has been reported to be <12%.[37,61]

SLC22A12

The *SLC22A12* gene encodes URAT1, an essential urate transporter in proximal tubules that has a role in the apical absorption of urate[66] and is a target of both urico suric and antiuricosuric agents (Figure 2). Loss-of-function mutations in *SLC22A12* have been identified in patients with familial renal hypouricaemia[2,66] and several associations between *SLC22A12* variants, serum uric acid concentrations and gout have been reported (Table 2).[67–72] A Japanese study showed that an intron SNP of *SLC22A12* (rs893006) was associated with serum uric acid levels in Japanese men ($n = 326$).[67] Another study showed statistically significant associations between three different polymorphisms in the *N*-terminus of *SLC22A12* (–788T>A in the promoter region, C258T in exon 1 and C426T in exon 2) and reduced FEua levels in a German population.[68] The strongest association was found for the C426T mutation ($P = 0.0002$).[68] Variations in *SLC22A12* were also associated with gout in Mexican[69] and Asian populations.[70,71,73,74] The Wellcome Trust Case-Control Consortium (WTCCC) genome-wide scans did not show associations between known urate

transporter genes, including *SLC22A12,* and serum urate levels.[36] However, this lack of association might be attributable to poor tagging of the transporter genes by the gene array chip used by the consortium.[28,36] A subsequent meta-analysis of 14 GWAS (including the WTCCC studies) did show a significant association between *SLC22A12* and serum urate levels ($P = 2 \times 10^{-9}$).[32]

In populations with European ancestry, *SCLA22A12* might only account for 0.13% of serum uric acid variance, and the observed association might be the result of close linkage disequilibrium with the *SLC22A11* gene.[33] However, a novel rare nonsynonymous variant of *SLC22A12* with a large serum uric acid effect size (71.38 μmol/L) was identified as being associated with serum urate ($P = 2.7 \times 10^{-16}$), and the identification replicated, in a meta-analysis of data from GWAS of African American populations.[72] The variant SNP, rs12800450, caused a glycine-to-tryptophan substitution at position 65 (Gly65Trp) and had a minor allele frequency of 1%.[72]^{14}C-urate transport assays showed that the Gly65Trp mutant protein had reduced urate transport function compared with wild-type URAT1, suggesting that the mutation might lead to a reduction in urate absorption.[72]

Other reproducibly associated variants

Two large meta-analyses, each involving >28,000 participants, identified several other genome-wide genetic variants that are reproducibly associated with serum uric acid levels or gout (Table 3).[32,33] The first, carried out in 2009, showed associations between nine common genetic variant loci and serum uric acid concentrations—the previously discussed variants *SLC2A9* ($P = 5.2 \times 10^{-201}$), *ABCG2* ($P = 3.1 \times 10^{-26}$) and *SLC22A12* ($P = 2.0 \times 10^{-9}$), and six other variants: *SLC17A1* ($P = 3.0 \times 10^{-14}$), *SLC22A11* ($P = 6.7 \times 10^{-14}$), *SLC16A9* ($P = 1.1 \times 10^{-8}$), *GCKR* ($P = 1.4 \times 10^{-9}$), *LRRC16A* ($P = 8.5 \times 10^{-9}$) and near *PDZK1* ($P = 2.7 \times 10^{-9}$).[32] In 2010, six of these loci (*SLC2A9, ABCG2, SLC17A1, SLC22A11, CGKR* and *PDZK1*) were confirmed in a meta-analysis of five population-based cohorts of the CHARGE consortium.[33] Of the remaining three loci, *SLC22A12* was not considered to be an independent locus because of its proximity to *SLC2A11* and the genome-wide significance of *SLC16A9* and *LRRC16* was border line ($P = 1.7 \times 10^{-7}$ and 1.3×10^{-7} respectively).[33] How ever, a UK population-based study ($n = 7{,}795$) later con firmed the association between *SLC16A9,* but not *LRRC16*, and serum uric acid concentrations.[75] The CHARGE meta-analysis also identified the *R3HDM2–INHBC* region and *RREB1* loci as having genome-wide significance with serum urate levels.[33] Subsequently, a meta-analysis[72] and a GWAS[51] showed that 10 of the 11 loci that have been shown to influence serum urate concentration in individuals with European ancestry were significantly associated with serum uric acid or gout in African-American populations.

A reproducible genome-wide association between the *SLC17A3* loci, serum uric acid levels and gout has been shown in a white population.[37] *SLC17A1* and *SLC17A3* encode SLC17A1 (also known as NPT1) and SLC17A3 (also known as NPT4), respectively. These proteins are voltage-dependent, multispecific anion transporters that are expressed at the apical membrane of the proximal tubule and are thought to be involved in the apical secretion of urate.[76,77,78] Other identified substrates for these transporters include *p*-amminohippuric acid, bumetanide and estrone sulphate.[79] Coding polymorphisms in the *SLC17A1* (Arg138Ala) and *SLC17A3* genes (Val257Phe, Gly279Arg and Phe378Leu) that are associated with hyperuricaemia generate transport proteins with reduced function.[76,77,80] The scaffolding protein, PDZK1-interacting protein 1, interacts with the protein products of *SLC22A12* (which encodes URAT1), *SLC22A13, SLC5A8, SLC5A12, SLC22A11, SLC17A1* and *SLC17A3*.[81] Thus, PDZK1 might link the transporter proteins URAT1 (responsible for urate reabsorption) and SLC17A1 (responsible for secretion) into a complex that could potentially regulate urinary urate excretion (Figure 2).[41,81] PDZK1 variants that

are associated with gout and serum uric acid levels might affect the function of this putative regulatory complex.

MCT9, a monocarboxylic acid, sodium-dependent transporter protein that is expressed in the kidney, is encoded by *SLC16A9*. The substrate or substrates of this transporter are unknown. However, a meta-analysis showed that the rs12356193 SNP of the *SLC16A9* gene was associated with DL-carnitine and propionyl-L-carnitine concentrations as well as with serum uric acid levels.[32]

The *LRRC16A* gene codes for LRRC16A (also known as CARMIL), which is present in kidney and epithelial cells. This protein is a key inhibitor of actin capping protein and, therefore, a regulator of actin polymerization.[82] However, the underlying mechanism behind the association between LRRC16A and serum uric acid levels is not known. The biochemical mechanism underlying the association between SNPs of the *RREB1* and *INHBC* genes and serum uric acid levels is also unknown. *RREB1* encodes a zinc finger transcription factor (ras-responsive element-binding protein 1) that has been reported to regulate the androgen receptor and calcitonin gene,[83] whereas *INHBC* encodes a member of the transforming-β growth factor family, Inhibin β C chain.[84]

The *GCKR* gene encodes GCKR, which is predominantly expressed in the liver and does not seem to function in the direct handling of renal urate. In the liver, GCKR regulates glucokinase[75,85] by mediating the phosphorylation of glucose to glucose-6-phosphate, a precursor of liver glycogen synthesis and of *de novo* purine synthesis.[75,85] A deficiency in the activity of glucose-6-phosphatase causes glycogen storage disease type 1 (also known as von Gierke disease), which is characterized by hypertriglyceridaemia and hyperuricaemia.[75,85] The *GCKR* SNP rs780094 might affect both serum uric acid and triglyceride levels (which are associated with insulin resistance) via a common mediator.[75] Interestingly, *GCKR* is associated with insulin resistance,[32] glucose level, triglyceride level, and C-reactive protein,[86] which are components of metabolic syndrome.[75]

Potentially associated variants

Several other genes that might be associated with serum uric acid levels or gout have been identified (Table 4). An Icelandic study that involved whole-genome sequencing of 16 million SNPs for low frequency variants, showed that a risk allele of *ALDH16A1* was associated with an OR of 3.1 for gout ($P = 1.5 \times 10^{-16}$), which probably represents the largest single gene effect among recently discovered variants.[13] However, the *ALDH16A1* variant is rare (~1% in Icelandic and <1% in white populations) and is expected to have a limited population attributable risk compared with common variants such as those of *SLC2A9*. The results of the Icelandic study further confirmed an association between the previously identified genetic variants of *SLC2A9, ABCG2, SLC17A, SLC16A9, SLC22A11, GCKR*, and *INHBC*, and serum uric acid levels.[13] In addition, a novel variant (rs12129861) that associated with gout was identified in chromosome 1.[13] Other reported genetic polymorphisms that could potentially be associated with serum uric acid levels and gout include variants of *SGK1-SLC2A12*,[72] *ADRB3*,[87–89] *MTHFR*,[90–95] *PRKG2*[96] and TGFB1[97] (Figure 3).[32] Most of these genes can be considered candidate genes as they have not yet been validated in large-scale studies in separate populations.

Clinical utility of genetic variants

The common genetic variants identified in GWAS confer a modest risk of gout. However, an additive composite genetic urate score of high-risk alleles can confer up to a 41-fold increased risk for gout compared with individuals without any such alleles.[33] A similarly constructed nongenetic risk factor score (based on BMI, alcohol intake, diuretic use and

history of hypertension) conferred up to a 79-fold increased risk of gout in the US general population.[98] The serum uric acid variance explained by common genetic variants is small (~6% in the CHARGE meta-analysis),[33] particularly when compared with the 67% of serum uric acid variance that can be explained by nongenetic factors, such as serum creatinine level, metabolic syndrome components (including insulin resistance, waist circumference and systolic blood pressure) and FEua.[75]

The clinical utility of genetic variants or their composite genetic scores for gout remains unclear. Their utility for predicting gout seems limited because serum urate levels, which can be easily measured, effectively predict gout risk.[2] Furthermore, genetic scores would have limited utility in justifying initiation of urate-lowering therapy in patients with asymptomatic hyperuricaemia[37] because even onset of gout does not necessarily justify initiation of such therapy given the associated potential adverse effects.[99,100] Further studies are required to determine if genetic scores could be used to predict worse outcomes, such as tophaceous erosive gout, complications of gout, or responses to certain classes of antigout drugs, particularly uricosuric drugs that might target the urate transportasome.[29]

Urate and cardiovascular events

Serum uric acid levels and gout are both strongly associated with metabolic syndrome and risk of cardiovascular disease. However, whether these relations are causal is unclear.[2,33,101] In an attempt to answer this long-standing question, Mendelian randomization studies were included in some GWAS[102,103] and in the CHARGE meta-analysis.[33] In these studies the genetic urate score (rather than serum uric acid concentration) was used as the exposure variable for a potential causal role of serum uric acid in the development of cardiovascular–metabolic events.[2,33,101,104] The Mendelian randomization studies could be thought of as natural randomized trials of the effects of genetically determined variation in serum uric acid concentration on cardiovascular–metabolic outcomes because the genes are randomly assigned during gamete formation and this assignment is unlikely to be affected by nongenetic or environmental factors.

The CHARGE Mendelian randomization analyses showed that genetically-determined serum uric acid levels (assessed using the urate genetic score) were not associated with blood pressure, glucose levels, renal function, chronic kidney disease or coronary heart disease.[33] These findings did not support a causal role for serum uric acid in the development of cardiovascular disease or metabolic syndrome. However, the urate genetic scores were strongly associated with gout, confirming a causal relationship.[33] Similarly, a Mendelian randomization analysis of *SLC2A9*, which used a Bayesian approach, found no evidence for a casual role of serum uric acid in metabolic syndrome.[102] A similar lack of association between urate genetic variants and cardiovascular and metabolic outcomes has been shown in other GWAS.[31,34,39]

By contrast, a Mendelian randomization study published in 2012, showed that serum uric acid levels determined by *SLC2A9* alleles were associated with systolic blood pressure in 526 Amish adults who were not receiving diuretic or antihypersensitive drugs.[103] The difference in findings might be related to differences in study design. The participants in the Amish study received standardized diets and 24-h ambulatory blood-pressure monitoring,[103] whereas the CHARGE study participants received a liberal diet and single-visit blood-pressure measurement.[33] The contrasting findings of the two studies suggest the potential importance of a controlled setting and homogenous population when examining secondarily mediating gene effects in Mendelian randomization analyses.[103]

Pharmacogenetics of allopurinol

The most commonly used urate-lowering antigout drug, allopurinol, is associated with rare (affecting ~0.2% of patients), but severe, hypersensitivity reactions that are fatal in 25% of cases.[105] Pharmacogenetic studies have shown a strong association between *HLA-B*5801* and allopurinol-induced Steven–Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) in Korean, Han Chinese, Japanese, Thai[106–110] and European populations.[111] A meta-analysis based on these studies showed that patients who expressed the *HLA-B*5801* allele had an 80–97-fold increased risk of developing SJS or TEN in response to allopurinol compared with patients who did not express the allele.[112]

A GWAS that included 14 Japanese patients who had allopurinol-related SJS or TEN and 991 ethnically matched healthy controls, confirmed the strong association between the *HLA-B*5801* locus and allopurinol-related hypersensitivity reactions (OR 62.8; $P = 5.388 \times 10^{-12}$).[113] The study also identified several other SNPs in *BAT1, HCP5, MICC* and *PSORS1C1* genes, which were significantly associated with allopurinol-related SJS or TEN (OR >61; $P < 4.62 \times 10^{-8}$ for all associations).[113] The *PSORS1C1* SNP, rs9263726, was in absolute linkage disequilibrium with *HLA-B*5801*.[113] If these findings are confirmed in other populations, rs9263726, which can easily be typed, could be a useful biomarker for prediction of allopurinol-related SJS or TEN.[113]

Conclusions

GWAS have led to a remarkable increase in replicable genetic association data for serum uric acid and gout. Reduced renal excretion of urate is the major cause of hyperuricaemia and gout and most of the common genes discovered in GWAS are involved in the renal urate-transport system. The genes for the urate transporters, GLUT-9 and ABCG2, which are important modulators of uric acid levels, consistently associate with serum uric acid levels and gout. Although the GWAS association data for *SLC22A12 (*which encodes URAT1*)* have been less impressive, many layers of evidence indicate that URAT1 is an essential component of renal urate handing. Loss-of-function mutations in the absorptive transporter genes *SLC22A12* or *SLC2A9* lead to a dominance of urate secretion and hypouricaemia, whereas loss-in-function or reduction-in-function mutations in the secretory urate transporter genes, *ABCG2, SLC17A1* or *SLC17A3*, cause hyperuricaemia. These findings indicate that serum uric acid levels are largely determined by the relative balance between urate absorption and secretion across the proximal tubule. Most of the other replicated genetic variants discussed in this Review require further functional characterization. However, these genetic data add considerably to our understanding of the pathogenesis of hyperuricaemia and gout. Future research directions might include replication in other ethnic cohorts, fine mapping and resequencing, functional studies of the identified genetic variants and evaluation of potential interactions between genes and key environmental factors.[2,28,100,114] Genetic markers that are associated with severe gout (such as tophaceous erosive gout), other complications of gout, or efficacy and adverse reactions to antigout drugs should also be evaluated.

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Key points

- The majority of the genes that associate with hyperuricaemia and gout in genome-wide association studies have been implicated in the renal urate-transport system
- Genetic variation explains only a modest level of variance 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 renal proximal tubule
- The clinical utility of testing for urate-associated genes seems limited because serum urate levels themselves can effectively predict gout risk at a low cost
- Urate-associated genes and genetically determined urate levels have been largely unassociated with cardiovascular or metabolic outcomes, suggesting that serum uric acid does not have 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, suggesting clinical utility of testing for these alleles

Review criteria

A search for original articles published between 1965 and 2012 and focusing on the genetics of hyperuricaemia and gout was performed in MEDLINE and PubMed. The search terms used were “uric acid”, “urate”, “urate transporters”, “hyperuricaemia”, “gout”, “gene”, “genetic”, and “loci”, alone and in combination. All articles identified were English-language, full-text papers. We also searched the reference lists of identified articles for further relevant papers.

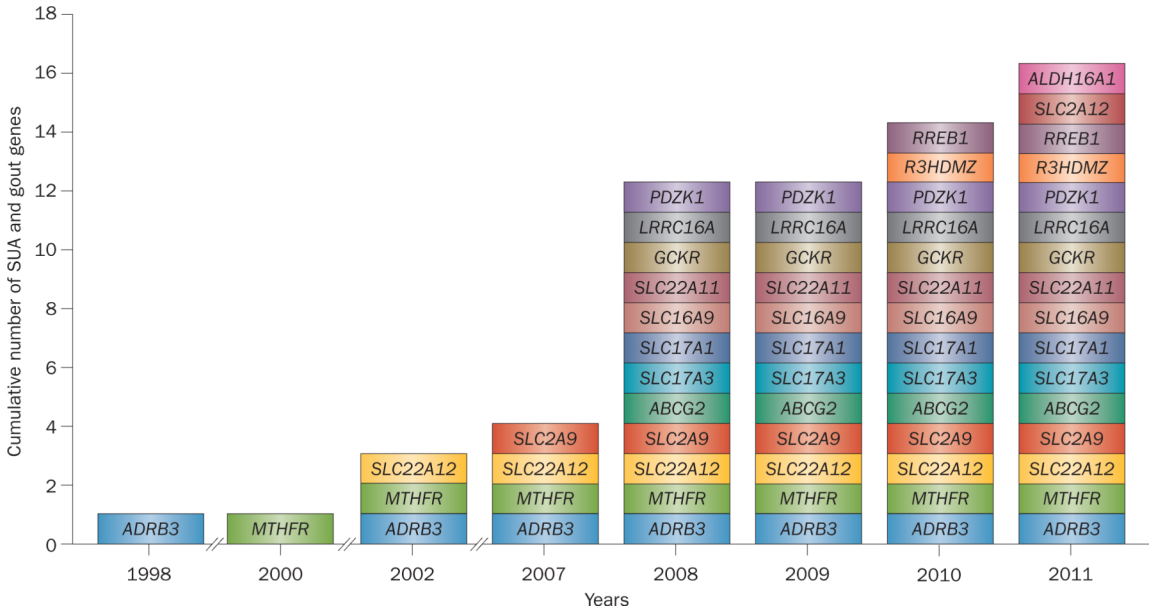

Figure 1.

Genetic variants implicated in the pathogenesis of hyperuricaemia or gout. Discovery timeline showing cumulative number of genes discovered from 2008–2011. Abbreviation: SUA, serum uric acid.

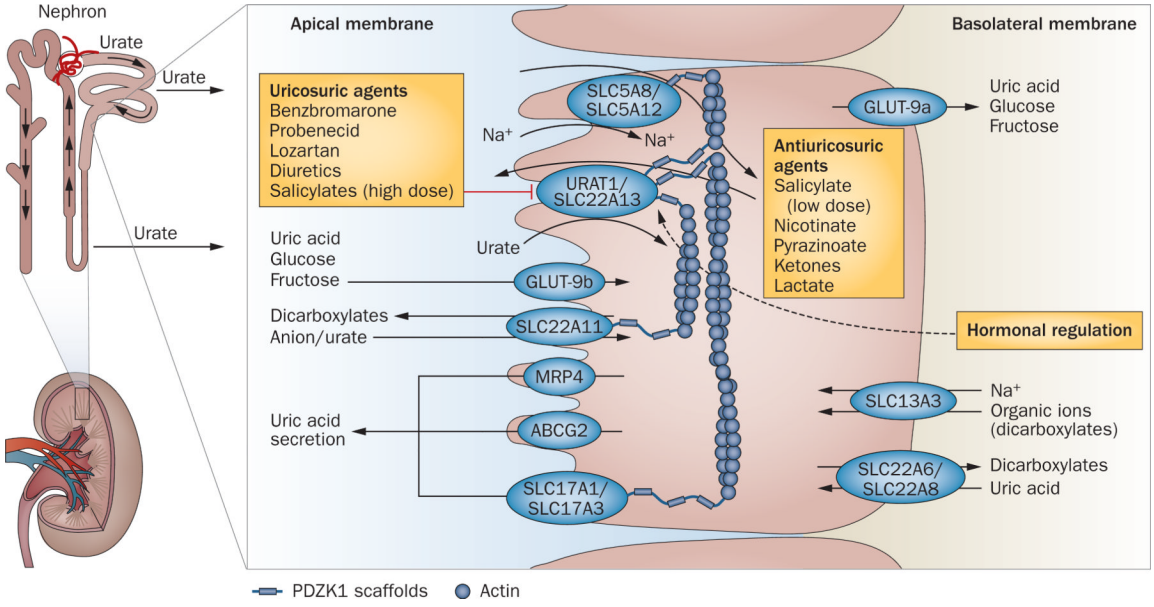

Figure 2.

The uric acid transportasome. Urate transporters in renal proximal tubules are involved in the secretion and reabsorption of urate. The balance between these processes determines the net proximal renal excretion. Urate secretion involves SLC22A6 and SLC22A8, which transport uric acid into the epithelial cell across the basolateral membrane, and URAT1, SLC22A13, SLC17A1, SLC17A3, MRP4 and ABCG2, which transport uric acid out of the epithelial cell across the apical membrane. Reabsorption of urate across the apical membrane involves the urate-anion exchangers URAT1 and SLC22A13, which facilitate the entry of urate into the cell in exchange for monocarboxylates (transported into the cell by the sodium-dependent transporters SCL5A8 and SCL5A12) as well as SLC22A11, which exchanges urate and dicarboxylates (transported into the cell by SLC13A3). Antiuricosuric drugs can serve as the exchanging anion for URAT1 and, therefore, enhance urate transport. URAT1 is inhibited by uricosuric agents and might be regulated by hormones. The glucose transporter GLUT-9 also has an important role in reabsorption of urate; GLUT-9b transports uric acid across the apical membrane and GLUT-9a transports uric acid out of the epithelial cell across the basolateral membrane. The scaffolding protein, PDZK1, is involved in the assembly of a transport complex in the apical membrane.

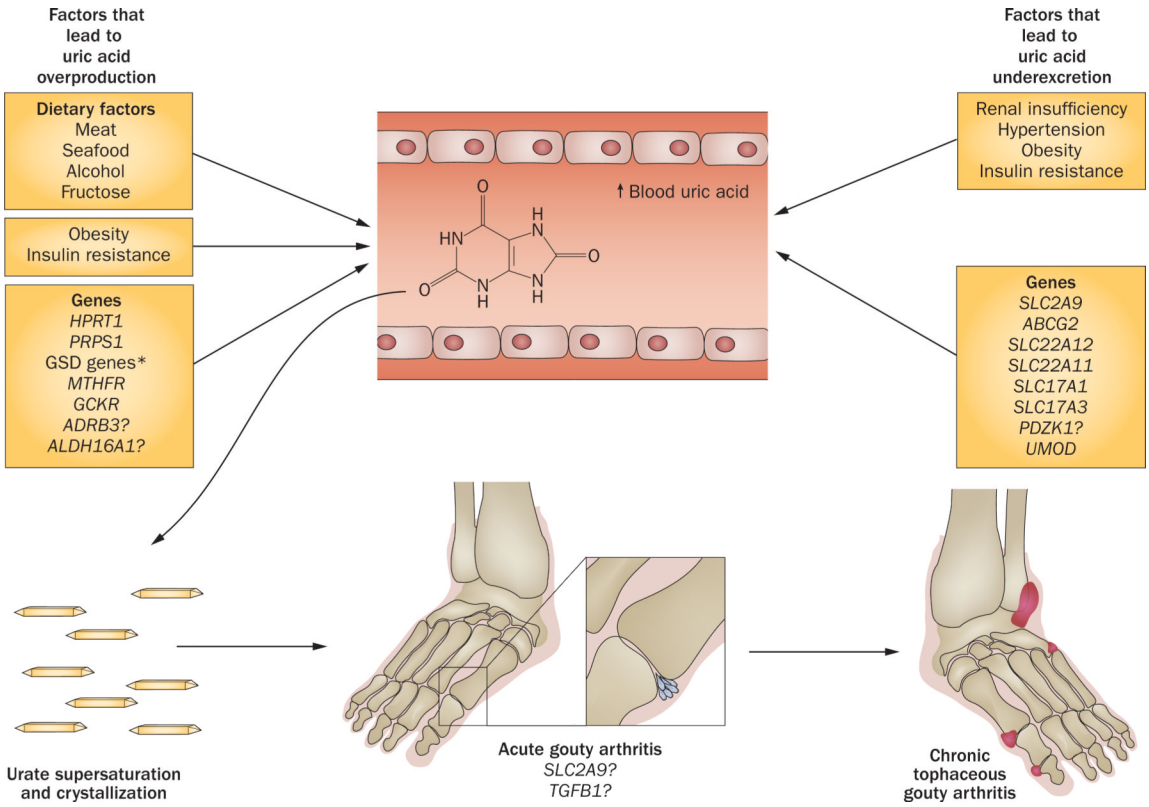

Figure 3.

The pathogenesis of hyperuricaemia and gout. Genetic and environmental factors are juxtaposed with the two major mechanisms that lead to hyperuricaemia—exogenous and endogenous overproduction of uric acid and underexcretion of urate. Hyperuricaemia results in the formation of monosodium urate crystals in oversaturated tissue fluids. As well as urate concentration (serum uric acid levels >404.5 μmol/L), crystallization is dependent on pH, temperature and other factors.[2] Stimulation of the NALP3 inflammasome and other humoral and cellular inflammatory mediators by monosodium urate crystals results in acute gouty arthritis.[115] Chronic cumulative urate crystal formation in tissue fluids leads to deposition of monosodium urate crystals in the synovium, cartilage, tendons and soft tissues, resulting in tophi formation and chronic tophaceous gouty arthritis. The vast majority of newly identified common genetic variants that are associated with hyperuricaemia and/or gout are involved in urate renal excretion. However, some of these variants are also expressed in extrarenal tissues and might be involved in the regulation of serum urate homeostasis (*ABCG2*) or the development of monosodium-urate-crystal-induced inflammation and arthritis (*SCL2A9, TGF-β*).*Including *CPT2, AMP1, ACDS* and *ALDOB*. Abbreviation: GSD, glycogen storage disease.

Table 1

Mendelian syndromes associated with hyperuricaemia and gout

Syndrome	Gene	Chromosome	Inheritance	Phenotype
Congenital errors of purine metabolism				
Hypoxanthine guanine phosphoribosyl transferase-related disease[9]	*HPRT1*	Xq26.2–q26.3	XD	Neurological dysfunction, hyperuricaemia, gout
Phosphoribosyl pyrophosphatase synthetase-related disease[22]	*PRPS1*	Xq22.3	XD	Hyperuricaemia, gout, neurological impairment
Excessive cell death and urate generation				
Glycogen storage disease-Ia[12]	*G6PC*	17q21.31	AR	Growth retardation, lactic acidosis, hypoglycaemia, hepatomegaly, hyperuricaemia, gout
Glycogen storage disease-Ib[12,13]	*SLC37A4*	11q23.3	AR	Growth retardation, lactic acidosis, hypoglycaemia, hepatomegaly, hyperuricaemia, gout
Glycogen storage disease-III[12,13]	*AGL*	1q21.2	AR	Early-onset hyperuricaemia, gout
Glycogen storage disease-V[12]	*PYGM*	11q13.1	AR	Early-onset hyperuricaemia, gout
Glycogen storage disease-VII[12,14]	*PFKM*	2q13.11	AR	Early-onset hyperuricaemia, gout
Late-onset carnitine palmitoyltransferase II deficiency[116]	*CPT2*	1p32.3	AR	Rhabdomyolysis, myoglobinuria, hyperuricaemia, gout
Myoadenylate deaminase deficiency[15]	*AMPD1*	1p13.2	AR or AD	Myopathy, hyperuricaemia, gout
Short chain, acyl-CoA dehydrogenase deficiency[16]	*ACADS*	12q24.31	AR	Metabolic acidosis, neurological impairment, myopathy, hyperuricaemia, gout
Fructose-1-phosphate aldolase deficiency[17]	*ALDOB*	9q31.1	AR or AD	Fructose intolerance, liver failure, renal tubulopathy, growth retardation, hyperuricaemia, gout
Reduced renal excretion of uric acid				
Medullary cystic kidney disease, type 1[18]	Unknown	1q21	AD	Variable penetrance, renal dysfunction, hypertension, gout
Medullary cystic kidney disease, type 2[19,20]	*UMOD*	16p12.3	AD or AR	Progressive renal dysfunction, variable hyperuricaemia, early-onset gout
Familial juvenile hyperuricemic nephropathy[21]	*UMOD*	16p12.3	AD	Progressive renal dysfunction, variable hyperuricaemia, early-onset gout

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; XD, X-linked dominant.

Table 2

SLC2A9, ABCG2 and *SLC22A12* variants associated with serum uric acid levels, FeUA and gout

Variant	Location	Phenotype	Populations
SLC2A9 (chromosome 4)			
rs1014290	Intron 3	SUA, FeUA, gout	European ancestry[34]
rs6449213	Intron 4	SUA, FeUA, gout	White,[34–37,43] African American[51,72]
rs16890979	Exon 6	SUA, gout	White,[37,42,44] African American,[72] Amish[55]
rs734553	Intron 6	SUA, gout	White,[32,39,44] Icelandic,[13] African American[72]
rs7442295	Intron 6	SUA, gout	White [35,38,39,44]
rs737267	Intron 7	SUA, FeUA, gout	European ancestry[34,44]
rs6855911	Intron 7	SUA, gout	White,[35,38,39,44] African American[72]
rs13129697	Intron 7	SUA, gout	White,[33,44] African American[72]
rs2241480	Intron 8	SUA, gout	European ancestry[72]
rs7663032	Intron 9	SUA, gout	African American,[72] Croatian[44]
rs3775948	Intron 9	SUA	Croatian,[44] African American[51]
rs16890979	Intergenic	SUA, gout	White,[37] Amish,[55] Croatian,[44] Pacific Islander,[42] New Zealander[42]
rs717615	Intergenic	SUA	Croatian[44]
rs6856396	Intergenic	SUA	African American[51]
rs10489070	Intergenic	Gout	Amish[55]
ABCG2 (chromosome 4)			
rs2231137	Exon 2	SUA	Japanese[63]
rs72552713 (Q126X)	Exon 4	SUA, gout	Japanese[63]
rs2231142 (Q141K)	Exon 5	FeUA, SUA, gout	White,[32,37,39,44,62] African,[37,72] Chinese,[60] Icelandic,[13] Japanese,[59,63] Pacific Islander,[61] New Zealander[31,61]
rs2199936	Intergenic	SUA	White [32,33,44]
SLC22A12 (chromosome 11)			
rs11231825	Exon 1	FeUA, SUA	Chinese,[70] White,[32,68] African American[72]
rs3825016	Exon 2	FeUA	German[68]
rs12800450	Exon 2	SUA	African American[72]
rs161109885	Intron 3	SUA	Chinese[73]
rs893006	Intron 4	SUA	Japanese,[67] Chinese[71]
rs1529909	Intron 4	FeUA, SUA	Korean[74]
rs475688	Intron 4	Gout	Chinese,[70] Solomon Islander[70]
rs17300741	Intron 4	SUA	European[32,75]
rs7932775	Exon 8	SUA, FeUA, gout	German,[68] Chinese,[70,73] Solomon Islander[70]
rs505802	Intergenic	SUA	European,[32,44] African American[72]
rs11602903	Intergenic	FeUA, SUA	German,[68] Chinese[73]

Abbreviations: FeUA, fractional excretion of urate; SUA, serum uric acid.

Table 3

Other* genetic variants associated with serum uric acid levels and gout

Variant	Location	Phenotype	Populations
SLC16A9 (chromosome 10)			
rs12356193	Intron 1	SUA	European,[32] Icelandic[13]
SLC17A1 (chromosome 6)			
rs1165196	Exon 7	SUA, gout	White,[33] Icelandic,[13] Japanese[37,117]
rs1183201	Intron 10	SUA	European[32]
rs1179086	Intron 12	Gout	Japanese[117]
rs3757131	Intron 12	Gout	Japanese[117]
rs11751616	Intergenic	SUA	African American[72]
rs2051541	Intergenic	SUA, gout	European ancestry[72]
SLC17A3 (chromosome 6)			
rs1165205	Intron 1	SUA	White[37]
SLC22A11 (chromosome 11)			
rs17300741	Intron 4	SUA	European[32]
rs10792443	Intron 4	SUA, gout	European ancestry[72]
rs2078267	Intron 6	SUA, gout	White,[33] Icelandic[13]
GCKR (chromosome 2)			
rs780094	Intron 16	SUA	European[32,75]
rs780093	Intron 17	SUA, gout	White,[33] Icelandic[13]
rs814295	Intron 17	SUA, gout	African American[72]
LRRC16A (chromosome 6)			
rs9467527	Intron 12	SUA	African American[72]
rs742132	Intron 30	SUA	European[32,75]
PDZK1 (chromosome 1)			
rs882211	Intron 1	SUA, gout	African American[72]
rs12129861	Intergenic	SUA	European,[32,38] Icelandic[13]
rs1967017	Intergenic	SUA, gout	White[33]
R3HDM2-INHBC region (chromosome 12)			
rs1106766	Intergenic	SUA	White,[33] Icelandic[13]
RREB1 (chromosome 6)			
rs675209	Intergenic	SUA	White,[33] Icelandic,[13] Croatian[44]

Abbreviation: SUA, serum uric acid.

*In addition to *SLC2A9, ABCG2* and *SLC22A12* variants (Table 2).

Table 4

Genetic variants potentially associated with serum uric acid levels and gout

Variant	Phenotype	Potential functional mechanism	Populations
ADRB3 (chromosome 8)			
Trp64Arg	SUA	Might cause reduced lipolysis and increased adipose tissue that could result in insulin resistance	Korean,[88] Spanish,[87] Italian,[95] Japanese,[89] Chinese[95]
rs4994	Gout	Unknown	Chinese[94]
MTHFR (chromosome 1)			
Cys677Thr	SUA	Might cause increased *de novo* synthesis of purines	Japanese,[90,92] Korean,[91] Iranian,[118] Brazilian[93]
PRKG2 (chromosome 4)			
rs10033237	Gout	Might cause increased renin activity	Taiwanese[96]
rs7688672	Gout	Might cause increased renin activity	Taiwanese[96]
rs6837293	Gout	Might cause increased renin activity	Taiwanese[96]
SGK1-SLC2A12 Locus (chromosome 6)			
rs9321453	SUA	Unknown	European ancestry, African American[72]
ALDH16A1 (chromosome 19)			
Cg1580C>G	SUA, gout	Might be involved in purine metabolism	Icelandic[13]
Chr 1-centromere (chromosome 1)			
Chr1_142697422	SUA, gout	Unknown	Icelandic[13]
TGFB1 (chromosome 19)			
869T/C	Tophi formation	Might regulate local inflammatory responses and/or tophi formation	Taiwanese[97]

Abbreviation: SUA, serum uric acid.