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Review

The genetic basis of hyperuricaemia and gout

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ABSTRACT

Gout results from elevated urate concentrations in the blood (hyperuricaemia). When super-saturation of urate is reached, monosodium urate crystals form within the joint. In some individuals, these crystals elicit a painful self-limiting inflammatory response that is characteristic of acute gouty arthritis. The most important cause of hyperuricaemia is reduced excretion of uric acid in the urine. Uric acid excretion is coordinated by a suite of urate transport molecules expressed in the renal collecting tubules, and is a key physiological checkpoint in gout. Other checkpoints in gout are hepatic production of urate, monosodium urate crystal formation, and initiation of the acute inflammatory response. Genome-wide association scans for genes regulating serum urate concentrations have identified two major regulators of hyperuricaemia– the renal urate transporters SLC2A9 and ABCG2. The risk variants at each gene approximately double the risk for gout in people of Caucasian ancestry, with SLC2A9 also resulting in higher risk for gout in people of Polynesian ancestry, a diverse population characterized by a high prevalence of gout. Ongoing genetic association studies are identifying and confirming other genes controlling serum urate concentrations; although genome-wide association studies in gout *per se* await recruitment of suitable case sample sets.

1. Introduction

Gout is the most common form of inflammatory arthritis affecting men, occurring in 1-2% of Caucasian men in Westernized countries. The central biochemical cause of gout is excess urate. In most mammals urate is degraded by uricase to allantoin, which is highly soluble and readily excreted in the urine. During the Miocene period, two parallel mutations occurred in early hominids that disabled the uricase gene, resulting in higher serum urate concentrations [1]. The parallel mutations suggest that inactivating the uricase gene was selectively advantageous to early hominids, possibly due to one, or a combination, of: the anti-oxidant activity of uric acid compensating for vitamin C deficiency; the ability of uric acid to maintain blood pressure under low-salt dietary conditions; the adjuvant activity of uric acid. Hyperuricaemia is the key predictor for development of gout – elevated urate above super-saturation concentrations [6.8 mg/dL at physiological pH and temperature] leads to the formation of monosodium urate (MSU) crystals within joints and subcutaneous tissues with the development of very painful attacks of gouty arthritis. Early gouty arthritis is characterized by recurrent episodes of self-limiting acute inflammatory attacks of monoarthritis. Subsequently, gout progresses with more frequent attacks that involve multiple joints. In some patients, chronic tophaceous disease may develop with progressive joint destruction and disability [2].

2. Key checkpoints in gout pathogenesis (Fig. 1)

2.1. Urate production

Urate is a product of hepatic purine metabolism, produced through metabolism of ingested purines (de novo synthesis) and endogenous metabolism of purines (salvage pathways). Hyperuricaemia may occur as a result of urate over-production, due to acquired causes such as high purine diet, fructose ingestion, alcohol intake, and myeloproliferative disorders, and also rare genetic causes such as hypoxanthine-guanine phosphoribosyltransferase (HPRT) deficiency and PRPP synthetase (PRS) superactivity. Fructose ingestion increases urate production by increasing hepatic ATP degradation to AMP, a urate precursor [3]. Recent studies have demonstrated a strong relationship between ingestion of fructose-containing beverages and both hyperuricaemia and gout [4,5].

2.2. Uric acid excretion

The major regulator of serum urate is renal excretion of uric acid [6,7]. In humans, net reabsorption of uric acid into the blood predominates owing to less excretion of uric acid than is filtered

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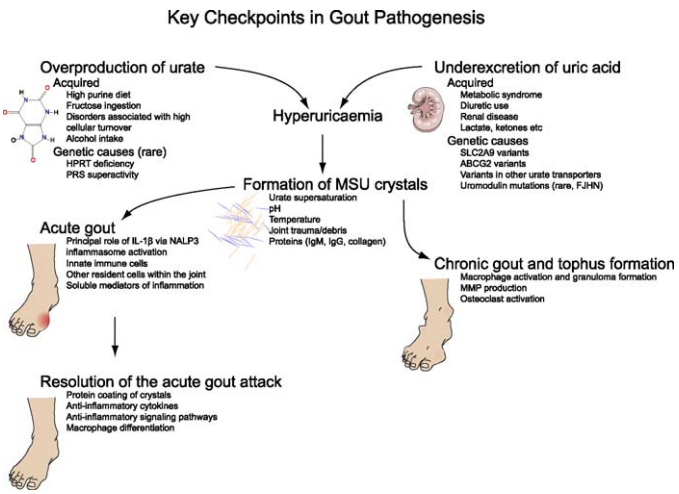

Fig. 1. Key checkpoints in gout pathogenesis.

at the glomerulus. This renal exchange is mediated by specialised molecules expressed in renal proximal tubule cells [8] (Fig. 2). Identified molecules include the fructose transporter SLC2A9 (GLUT9) [9], urate transporter 1 (URAT1; [10]), organic anion transporters 1,3,4 (OAT1, OAT3, OAT4), multi-drug resistance protein 4 (MRP4), sodium-coupled monocarboxyl transporters SMCT1,2, and human ATP-binding cassette, subfamily G, 2 (ABCG2) [11]. Variants of SLC2A9 exchange uric acid with fructose and glucose from the proximal tubule lumen across the apical and basolateral membranes, leading to net reabsorption of uric acid [12]. SLC2A9 is inhibited by the uricosuric agent benzbromarone, but not by the commonly used uricosuric probenecid [9]. URAT1 is substrate specific (compared to the multispecific OAT1 and OAT3) and is also inhibited by uricosuric drugs such as benzbromarone and probenecid [10]. OAT4 is a low-affinity assymetric urate transporter that facilitates diuretic-associated hyperuricaemia, also inhibited by benzbromarone and probenecid [13]. MRP4 is an ATP-dependent efflux pump for urate. ABCG2 is a secretory urate transporter in the proximal tubule [11], currently there are no published data on effects of uricosuric drugs on ABCG2 activity. As described later, genetic variants in these genes have been associated with serum urate levels and gout.

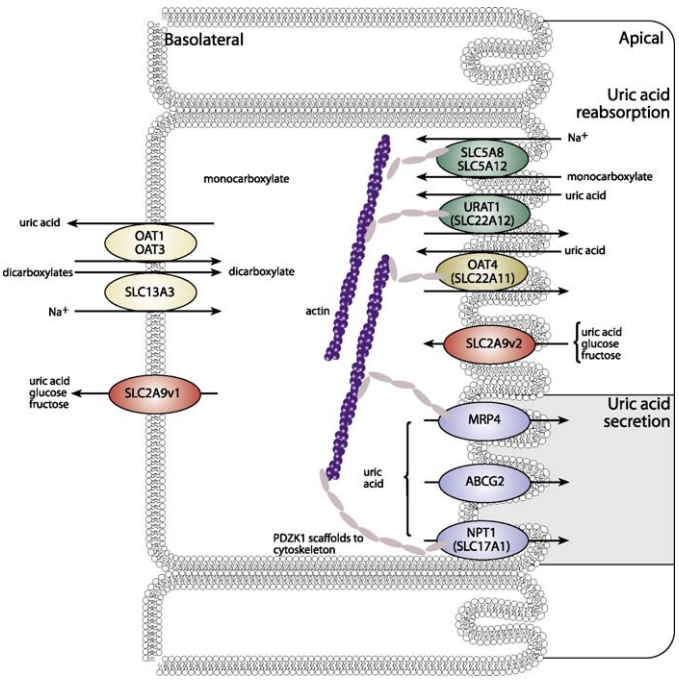

Fig. 2. The uric acid transportasome. Current understanding of uric acid transport in the proximal renal tubule. Monocarboxylates accumulate in the tubular cell through sodium-dependent monocarboxylate transporters SLC5A8 and SLC5A12, and dicarboxylates through SLC13A3. Uric acid enters the cell in exchange for monocarboxylate via apical URAT1 and for dicarboxylate via apical OAT4. Apical SLC2A9v2 plays a significant role in uric acid reabsorption, the reabsorbed uric acid exiting the cell through basolateral SLC2A9v1. For efflux of uric acid into the lumen, MRP4 and a voltage-driven organic anion transporter (vOAT1/NPT1) are candidates. OAT1 and OAT3 are known to transport uric acid, although the direction of transport is not clear. ABCG2 is a unidirectional transporter expressed on the apical membrane. PDZK1 is a scaffolding protein involved in assembly of a transporter complex in the apical membrane. Genetic variation in SLC2A9, ABCG2, URAT1, NPT1, OAT4 and PDZK1 is associated with serum urate levels and gout.

2.3. Formation of MSU crystals within the joint, inflammation and resolution of inflammation, tophus formation and bone erosion

There are a number of other checkpoints in gout, summarized here, for which no consistently replicated genetic associations have been described. Although hyperuricaemia is the strongest single risk factor for development of gout and is universally present in patients with gout, not all individuals with hyperuricaemia develop gout. It may be that certain individuals are at greater risk of developing MSU crystals within the joint [14], for example the presence of certain proteins such as immunoglobulin (particularly IgM) and insoluble collagen, and the presence of debris within the synovial cavity that can provide a nucleus for crystal development [15]. Patients with gout typically present with self-limiting bouts of severe joint inflammation resulting from a highly orchestrated reaction. Recent work has emphasized the importance of the innate immune response in regulating this response, and in particular, the initiation of acute inflammation through NALP-3 inflammasome activation by MSU crystals causing release of mature interleukin (IL)-1β, with subsequent release of IL-8, leading to recruitment of inflammatory cells within the joint [16]. There are functional genetic variants of *NALP3* and *CARD8*, components of the inflammasome, implicated in other inflammatory diseases [17], but yet to be evaluated in gout. MSU crystals are frequently identified in asymptomatic, uninflamed joints in patients with hyperuricaemia [14], suggesting that additional local or systemic factors can regulate the inflammatory response to existing intra-articular MSU crystals, leading to suppression of the acute gout attack. Factors contributing to the resolution phase of the acute gout attack are less well defined, but putative mechanisms include release of anti-inflammatory cytokines such as TGF-β, induction of anti-inflammatory signaling pathways such as PPARγ, and alterations in macrophage differentiation [18]. In the presence of prolonged hyperuricaemia, some patients develop tophi within the joint and soft tissues. These lesions represent a foreign body granulomatous response to MSU crystals and may invade bone, leading to bone erosion and joint damage [2]. It is of interest that tophus formation is not consistently present in all patients with longstanding hyperuricaemia and gout, suggesting that additional factors may regulate the development of these lesions.

3. The genetic basis for hyperuricaemia and gout

The previous two years have seen considerable inroads into the understanding of the genetic basis of hyperuricaemia and gout (Table 1). The Human Genome Project, large population-based cohorts and technologies enabling massively parallel assessment of genomic variation have enabled genome-wide association scanning [19]. This advance in knowledge has come from genome-wide association scans (GWAS) examining genetic factors controlling serum urate concentrations, a simple phenotype to measure, yet a

Table 1
Summary of replicated genetic associations with gout and contributing phenotypes.

Gene[a]	Phenotype	Effect size (odds ratio)[b]	Population	Molecular mechanism	Reference
SLC2A9/GLUT9	Serum urate	Not applicable	Caucasian	An influence on the relative levels of two SLC2A9 isoforms, one expressed on the basolateral and the other on the apical membrane of the renal collecting tubule	[12,21–24]
	Hyperuricaemia	1.7–1.9	Caucasian		[12]
	Gout	1.3–5.0	Caucasian, Solomon Island, NZ Maori and Pacific Island, Chinese		[12,21,24–26,53]
ABCG2	Serum urate	Not applicable	Caucasian	The 141Lys risk variant results in an ABCG2 molecule with 53% less uric acid secretory activity	[24]
	Gout	1.7–2.0	Caucasian, African-American Western Polynesian		[11,24,28]
SLC22A12/URAT1	Reduced renal uric acid excretion	1.4	Caucasian	A possible influence on isoform levels	[8]
	Serum urate	Not applicable	Caucasian, Japanese		[8]
	Hyperuricaemia	1.4	Chinese		[8]
	Gout	1.2-1.8	Mexican-American, Solomon Island, Chinese		[34–36]
SLC17A1/NPT1	Serum urate	Not applicable	Caucasian	Unknown	[24]
	Gout	1.2–1.9	Caucasian Japanese		[24,33]
β-3-adrenergic receptor [*ADRB3*]	Serum urate	Not applicable	Chinese	The 64Arg variant is associated with higher serum urate levels in three of four studies. This may induce insulin resistance as a result of lower lipolysis and increased adipose tissue	[8]
	Hyperuricaemia	1.1–2.4	Korean, Italian, Japanese		[8]
Methylene tetrahydrofolate reductase [*MTHFR*]	Hyperuricaemia	1.5–1.7	Korean, Iranian, Japanese	The 677T allele is associated with hyperuricaemia in 3 studies. It is possible that this variant allows greater availability of 5,10-methyltetrahydrofolate for *de novo* synthesis of purines	[8]

[a] Restricted to common variants (polymorphisms) of genes.
[b] For single copy of risk variant.

very important sub-phenotype in gout. To date, no GWAS for gout has been published.

3.1. SLC2A9

Li et al. [20] first reported association of the SLC2A9 gene with serum urate concentrations in Italian cohorts, rapidly replicated in a number of other GWAS for serum urate concentrations in population-based cohorts such as the Framingham Heart Study [12,21–24]. Genetic variation in *SLC2A9* explains up to 5% of variation in serum urate concentrations, a large effect in the context of genetic of complex phenotypes. Not unexpectedly, the same *SLC2A9* variants influence the risk for gout in Caucasian, with odds ratios from 1.3–2.2 depending on the procedure used for identification of cases and ascertainment of gout [12,21,24–26]. The functional variant(s) within *SLC2A9* have not been identified, but are likely to influence the relative expression levels of two SLC2A9 isoforms that differ by the length of their cytoplasmic domains [12,21]. The long form is expressed on the basolateral membrane of renal collecting tubule epithelial cells, whilst the short form is expressed on the apical membrane [27].

3.2. ABCG2

A non-synonymous single nucleotide polymorphism (*rs2231142*; Q141K) is the likely etiological variant explaining the association of *ABCG2* with gout [11,24]. The 141K allele confers a similar risk to gout as *SLC2A9*, approximately doubling risk in Caucasian [24,28]. This variant encodes an ABCG2 protein with 53% less urate transport activity [11], leading to a reduction in renal urate excretion. ABCG2 is also known as breast cancer resistance protein, functioning as an efflux pump with an influence on the pharmacokinetic profile of a variety of drugs. Consequently, there has been considerable work undertaken studying the biochemistry

and modulation of ABCG2. For example, ABCG2 mRNA levels are upregulated by statins in HepG2 cells [29]. This is promising in the context of improved therapies for gout. Both SLC2A9 and ABCG2 have been associated with gout in Polynesian populations, described in more detail later.

3.3. URAT1, NPT1 and other candidates in Caucasian

Meta-analysis of a number of GWAS, which included a total of 28,141 Caucasian individuals has revealed seven further genes associated, at a genome-wide level of significance ($P < 5 \times 10^{-8}$) with genetic control of serum urate concentrations [30]; renal urate transporters (*SLC22A12/URAT1, SLC22A11/OAT4, SLC17A1/NPT1*); a monocarboxylic acid transporter (*SLC16A9/MCT9*) that may be a renal sodium-dependent transporter that influences serum urate; *PDZK1* that encodes a scaffolding protein called PDZ domain-containing 1 known to interact with OAT4, URAT1 and NPT1 [31]; the LRRC16A locus; and the gene encoding glucokinase regulatory protein (*GCKR*). A follow-up study in a population-based cohort replicated association of *PDZK1, GCKR, SLC16A9* and *OAT4* with serum urate levels [32]. Both *URAT1* and *NPT1* have previously been genetically implicated in gout [33–36]. Of the other loci, *OAT4* and *PDZK1* are very strong candidates for gout risk factors. One recent follow-up study published in gout reported lack of association of *PDZK1, GCKR, LRRC16A, SLC16A9, SLC22A11/OAT4* and *SLC22A12/URAT1* in a German Caucasian sample set [37]. In this study, cases were not established by clinical examination, and controls were relatives of myocardial infarction patients. Together, these ascertainment strategies would decrease power to detect genetic association with gout. This is best illustrated by the ABCG2 data reported in the same study [37]; the odds ratio of 1.4 being considerably less than that reported using ACR criteria to ascertain Caucasian cases (OR = 2.0; [28]).

3.4. Relationship to other metabolic disease

Gout is strongly associated with obesity and metabolic syndrome. Adiposity and weight gain are important risk factors for development of gout, while weight loss is protective [38]. Both metabolic syndrome and type 2 diabetes are more common in patients with gout [39,40]. The relationship between gout and metabolic syndrome is thought to be mediated by hyperuricaemia; serum urate concentrations correlate with the degree of central adiposity and measures of insulin resistance, and insulin inhibits renal tubular uric acid excretion [41].

The association of *GCKR* with serum urate levels may provide a link between hyperuricaemia and other metabolic conditions; *GCKR* has also been associated with triglyceride and fasting glucose concentrations and risk of type 2 diabetes [42–44]. Interestingly, the association of GCKR with serum urate levels reported by van der Harst et al. [32] is attenuated by triglyceride levels, with the most plausible explanation being that *GCKR* affects both serum urate and triglyceride levels by a common unconfirmed mediator [32], that could be glucose-6-phosphate. GCKR controls the intracellular location and activity of glucokinase, and hence the hepatic production of glucose-6-phosphate, a precursor for *de novo* purine (uric acid) synthesis and the catabolic products of which are used for triglyceride synthesis via acetylCoA.

The genetic data do indicate that hyperuricaemia *per se*, considered in isolation of other interacting factors, is not an independent risk factor for type 2 diabetes or other obesity related quantitative traits – none of *SLC2A9, ABCG2, OAT4* or *NPT1* has yet been implicated as risk factors in type 2 diabetes or obesity.

The beta-3 adrenergic receptor and methylene tetrahydrofolate reductase genes have also been implicated in regulation of serum urate concentrations in more than one population [8] (Table 1). The beta-3 adrenergic receptor data are particularly intriguing, suggesting a genetic link between serum urate concentrations and insulin resistance, a frequent comorbid feature of gout. Study of these genes in other populations, including Caucasian, is needed.

3.5. Genetic factors associated with MSU crystal deposition and inflammatory response

The recent genetic findings confirm that renal excretion of uric acid is a major determinant of gout. However, there are other checkpoints in gout pathogenesis in which inherited genes may play a role in determining risk; hepatic production of urate, formation of MSU crystals, initiation and resolution of the inflammatory response to MSU crystals. To date, no genetic factors have been convincingly implicated in any of these processes, with strong statistical support and replication in multiple sample sets. The recent leap in understanding of the major renal urate transport genes that control serum urate concentrations largely resulted from the use of extant population-based cohorts in which serum urate concentrations had been measured, a straightforward phenotype to ascertain. The best approach for identification of risk factors for gout, outside from those that control serum urate concentrations, is genome-wide association studies in large cohorts of gout patients and controls. When such studies are done, it will be important to ascertain phenotype on the basis of American College of Rheumatology criteria [45] or, ideally, by aspirate-proven disease. Ascertainment criteria that rely on administrative data leads to misclassification of gout [46], and self-reported diagnoses are likely to be unreliable. Close attention to classification of gout in GWAS will be essential for the detection of weaker genetic effects. Use of a hyperuricaemic non-gout control group would increase the power of any such study in detecting genes involved in MSU crystal deposition and/or MSU inflammatory response.

4. Gout in Polynesia

Although the prevalence of gout is increasing worldwide [47], certain populations have higher rates of gout. Possible gouty erosions in skeletons from the 3000-year old Polynesian Lapita culture in Vanuatu have been reported [48]. Lesions consistent with gout were present in seven out of 20 skeletons (all male). The incidence of gout is 2% in men living on Tokelau, rising to 5% upon migration to New Zealand [49]. Both Tokelau cohorts had mean urate concentrations in the hyperuricaemic range. On Pukapuka in the Cook Islands, alcohol is rarely consumed, yet gout incidence is 5.3% in men and 2.4% on Rarotonga [50]. More than 40 years ago, it was recognised that "the people of the Pacific belong to one large gouty family" (Kellgren, 1964; quoted in [50]). The prevalence of gout in the New Zealand Māori and Pacific Island populations is the highest worldwide, 15% in men [2,51]. However, the one Pacific outlier is the early (pre-Westernised) New Zealand Māori population, in which gout was not described in 1882 [52]; "Gout, a rare disease; one which will probably be almost or quite unknown to young New Zealanders, who in appearance and build show scant tendency to the gouty diathesis, and in habits and mode of life do little to promote the spread of this most unnecessary malady. When gout does appear, it is always in the person of an immigrant."

The varying incidences of Pacific gout, moderate in traditional island populations, low in pre-European NZ Māori, and high in modern New Zealand Māori and Pacific Island populations, can be understood using a scenario of a strong genetic tendency modulated by the environment. A diet containing increased fructose is known to increase the risk of hyperuricaemia and gout [4,5] in the modern North American population. It is reasonable to speculate that a fructose-rich diet also promoted gout in ancient and

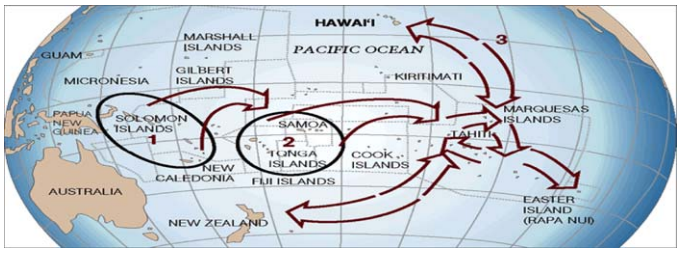

Fig. 3. The Polynesian migrations. The Polynesian culture originated approximately 3000 years ago in Tonga and Samoa from the Lapita culture within the Bismarck Archipelago. The eastern region of Polynesia from Hawaii in the north to New Zealand (Aotearoa) in the south had been settled by approximately 800 years ago. Within Polynesia there is a west to east decrease in Y-chromosome and mitochondrial DNA diversity [54], suggesting the occurrence of founder events. (1) Voyagers migrated outside Melanesia; (2) Polynesian culture developed *in situ* in the Samoa/Tonga region for as much as 1500 years before voyagers settled Eastern Polynesia ~500 AD; (3) Latest evidence suggests a multi-archipelago Polynesian homeland connected by active voyaging, a single language and culture. New Zealand (Aotearoa) may have been settled as late as 1200 AD. Map source: http://thehonoluluadvertiser.com/dailypix/2006/Mar/10/M121533310.GIF.

traditional Pacific Island populations, owing to the ready availability of fructose-rich foods, such as fruit and coconuts. Gout may have been rare in pre-European Māori owing to a diet consisting largely of *kaimoana* (seafood), birds and tuberous vegetables. The modern diet rich in processed sugar (and fructose) may impact severely on New Zealand Māori and Pacific Island people, who are genetically vulnerable to developing gout. The same variants in the fructose and uric acid transporter SLC2A9 (also known as GLUT9) that confer risk in Caucasian (*rs11942223,* for example) also confer an extremely high risk for gout in NZ Māori and Pacific Island sample sets, with a 500 percent increased risk (odds ratio = 5) conferred by the risk allele (compared with OR = 2 for Caucasian) [26]. Inheritance of dominantly protective variants at *SLC2A9* appears to be very important in New Zealand Maori and Pacific Island people [26]. In contrast, the Caucasian risk variants do not alter risk in Solomon Islander people, this population is monomorphic for the risk allele [53]. However, there is an independent non-synonymous variant in SLC2A9 (Arg265His) that confers about a 2-fold increased risk for gout in Solomon Islander people [53]. Collectively, the genetic results emphasize previous biochemical data that demonstrate the importance of renal urate transport in hyperuricaemia and gout, more so in people of Polynesian ancestry [6,7].

Strong association of the ABCG2 Q141K variant with gout has been reported in people of Western Pacific (Samoa, Tonga) ancestry (OR > 2.5) but not in people of Eastern Pacific ancestry (Cook Island and New Zealand Māori) (OR < 1.4) [28]. This is notable in the context of the high incidence of gout in both populations and the shared Polynesian ancestry and is likely to be caused by the founder events that occurred during Polynesian settlement of the Pacific (Fig. 3). These data emphasize the need to account for subpopulation differences when undertaking biomedical research in a group defined by a geographical region and shared ancestry but characterized by migratory events that create bottlenecks and altered genetic diversity in the founder populations.

4.1. Genetic causes of familial gout

Several genes with rare mutant alleles cause clinically distinct forms of familial gout. Mutations in the uromodulin gene cause familial juvenile hyperuricaemic nephropathy, a disease characterized by juvenile onset of hyperuricaemia, gout and progressive renal failure [55]. Uromodulin (Tamm-Horsfall glycoprotein) is the most abundant protein in urine, and plays a role in prevention of urinary tract infecton [56]. Mutations in the signal sequence of the renin gene result in early-onset hyperuricaemia and progressive renal failure by altering the intrarenal angiotensin system and kidney structure [57]. The relatively common A150P (*rs1800546*) mutation in the aldolase B gene (*ALDOB*) causes the recessive disease hereditary fructose intolerance (HFI) in approximately two-thirds of European cases [58] – many HFI patients also present with hyperuricaemia and gout. A deficiency in hypoxanthine guanine phosphoribosyltransferase (HPRT) activity leads to overproduction of urate, mutations in this enzyme result in gout and neurological symptoms (Lesch-Nyhan syndrome) [59]. Mutations in the X-chromosome gene phosphoribosylpyrophosphate synthetase can lead to superactivity, uric acid overproduction, gout and neurodevelopmental impairment in some cases [60]. Studying a possible role for these familial hyperuricaemia- and gout-causing genes in common gout is justified.

5. Conclusion

Major advances in the understanding of the genetic basis of hyperuricaemia have occurred in the last two years. These findings have primarily focused on renal excretion of uric acid. In particular, the importance of *SLC2A9* has been consistently demonstrated, highlighting the potential role of this transporter as a novel drug target. However, it should be noted that genetic variation in *SLC2A9* explains only ~5% of the total variation of serum urate concentrations in people of Caucasian ancestry, and that many other genes with smaller effects contribute. Furthermore, while hyperuricaemia is the major risk factor for gout, other factors contribute to formation of MSU crystals and the clinical presentation of acute gouty arthritis and chronic tophaceous disease. Large, well-characterized cohorts are needed to identify additional genetic risk factors for gout.

Conflict of interest

Neither of the authors has any conflicts of interest to declare.

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